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Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder

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Guidelines Update

Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013

Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, O'Donovan C, MacQueen G, McIntyre RS, Sharma V, Ravindran A, Young LT, Milev R, Bond DJ, Frey BN, Goldstein BI, Lafer B, Birmaher B, Ha K, Nolen WA, Berk M.

Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013.

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The Canadian Network for Mood and Anxiety Treatments published guidelines for the management of bipolar disorder in 2005, with updates in 2007 and 2009. This third update, in conjunction with the International Society for Bipolar Disorders, reviews new evidence and is designed to be used in conjunction with the previous publications.

The recommendations for the management of acute mania remain largely unchanged. Lithium, valproate, and several atypical antipsychotic agents continue to be first-line treatments for acute mania. Monotherapy with asenapine, paliperidone extended release (ER), and divalproex ER, as well as adjunctive asenapine, have been added as first-line options.

For the management of bipolar depression, lithium, lamotrigine, and quetiapine monotherapy, as well as olanzapine plus selective serotonin reuptake inhibitor (SSRI), and lithium or divalproex plus SSRI/bupropion remain first-line options. Lurasidone monotherapy and the combination of lurasidone or lamotrigine plus lithium or divalproex have been added as a second-line options. Ziprasidone alone or as adjunctive therapy, and adjunctive levetiracetam have been added as not-recommended options for the treatment of bipolar depression.

Lithium, lamotrigine, valproate, olanzapine, quetiapine, aripiprazole, risperidone long-acting injection, and adjunctive ziprasidone continue to be first-line options for maintenance treatment of bipolar disorder. Asenapine alone or as adjunctive therapy have been added as third-line options.

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Section 1. Introduction

In 2005, the Canadian Network for Mood and Anxiety Treatments (CANMAT) published guidelines for the management of bipolar disorder (BD) (1), followed by updates in early 2007 (2) and in 2009 [in collaboration with the International Society for Bipolar Disorders (ISBD)] (3). This update includes data published in 2009 through early 2012, and is designed to be used in conjunction with the 2005 CANMAT guidelines and previous updates (1–3).

The purpose of this update is to add previously unpublished material to the guidelines. This update is designed to be used with the previous iterations of the guidelines. As in the previous updates, the guidelines are divided into eight sections (Table 1.0) and the same numbering system has been used for the sections and tables in order to facilitate ease of use. New evidence is incorporated into the management recommendations, and changes to the recommendation tables have been clearly denoted with ***bold italics*** and a footnote, and have been described in the text. The objective is to ensure that the CANMAT guidelines for treatment of BD remain current and useful for the practicing clinician.

Central to this update are the tables showing first-line, second-line, third-line, and not-recommended treatment options. These tables may assist in the selection of treatment, while the text of this update and the previous guideline iterations provide the details of the evidence that was used to make the recommendations. Similarly, the treatment algorithms condense key management information into a decision-tree flow-chart; the clinician should begin by positioning the patient in the decision tree, and then follow the arrows for subsequent management suggestions.

Search strategies and methods to assess evidence were as described in the original guidelines (1). Evidence available only in abstract form was also considered in order to ensure that the recommen-

dations are as up to date as possible. The criteria for rating strength of evidence and making a clinical recommendation are shown in Tables 1.1 and 1.2.

We caution the readers that the evidence-based guidelines are limited by the data that are available. For instance, drugs that have patents are likely to have been more widely studied and their design was likely influenced by the goals of the sponsor to obtain approval. Generic drugs, although may be useful, may not have been widely studied because of lack of sponsorship, thus affecting their placement in the treatment algorithm. Finally, it is important to understand that the lack of evidence for a particular drug does not imply inefficacy or efficacy. Clinicians must exercise caution and choose treatments based on a careful risk–benefit analysis for each situation.

Section 2. Foundations of management

Epidemiology

Prevalence. The World Mental Health Survey Initiative, involving 61392 people in nine countries in North and South America, Europe, and Asia, reported lifetime (and 12-month) prevalence estimates of 0.6% (0.4%) for BD I, 0.4% (0.3%) for BD II, and 1.4% (0.8%) for subthreshold BD (4). However, there were large cross-national differences in rates, with the lifetime rates ranging from 0 to 1% for BD I, 0 to 1.1% for BD II, and 0.1 to 2.4% for subthreshold BD.

In the Canadian Community Health Survey–Mental Health and Well-Being (CCHS 1.2), the prevalence of BD was significantly lower among

Table 1.0. Overview of guideline sections

Section 1. Introduction
Section 2. Foundations of management
Section 3. Acute management of bipolar mania
Section 4. Acute management of bipolar depression
Section 5. Maintenance therapy for bipolar disorder
Section 6. Special populations
Section 7. Acute and maintenance management of bipolar II disorder
Section 8. Safety and monitoring
Closing statement
Disclosures
References

Table 1.1. Evidence criteria

1	Meta-analysis or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo condition
2	At least one DB-RCT with placebo or active comparison condition
3	Prospective uncontrolled trial with at least ten or more subjects
4	Anecdotal reports or expert opinion

Table 1.2. Treatment recommendation

First line	Level 1 or level 2 evidence plus clinical support for efficacy and safety
Second line	Level 3 evidence or higher plus clinical support for efficacy and safety
Third line	Level 4 evidence or higher plus clinical support for efficacy and safety
Not recommended	Level 1 or level 2 evidence for lack of efficacy

immigrant, compared to non-immigrant, subjects, but immigrants with BD were significantly less likely to report contact with mental health professionals (5).

Impact. A meta-analysis of 15 studies identified a high prevalence of lifetime suicide attempts both in patients with BD I (36.3%) and in those with BD II (32.4%) (6). In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (n = 4360), the completed suicide rate was 0.014 per 100 person-years (7). A large cohort study found that among men, the absolute risk of suicide was highest with BD (7.8%) compared to any other psychiatric condition, and among women, BD was associated with the second highest risk, at 4.8%, just below schizophrenia at 4.9% (8). Claims database data demonstrate the significant economic impact of suicide attempts, with one-year healthcare costs in the period post-attempt being more than double those in the year prior to an attempt (9).

The large, two-year, prospective, observational European Mania in Bipolar disorder Longitudinal Evaluation of Medication (EMBLEM) study (n = 2289) found high work impairment in 69% of patients at baseline and 41% at two years (10). Rapid cycling, high baseline work impairment, lower levels of education, recent admissions, mania symptom severity, and overall severity all predicted higher work impairment, while living in a relationship and independent housing predicted lower work impairment at follow-up. Similarly, the Understanding Patients' Needs, Interactions, Treatment, and Expectations (UNITE) global survey (n = 1300) revealed that only one-third of patients with BD were employed full-time (11). In the UNITE survey, treatment of depression, weight gain, and quality of life were identified by patients with BD as aspects of care most in need of improvement (11).

A meta-analysis of data from 12 trials (n = 1838) found that the self-esteem of patients with remitted BD was significantly lower than that of controls but significantly higher than that of patients with remitted major depressive disorder (MDD) (12). In addition, self-esteem may follow a fluctuating course during remission of BD.

In a health claims database, risk of arrest was associated with substance use, poor refill compliance, and prior arrest (13). Among patients treated with an atypical antipsychotic agent, there was a lower risk of arrest in those who had frequent outpatient visits (approximately monthly) compared to those who did not.

Course. In a sub-analysis of 771 patients in the two-year EMBLEM study, approximately one in three presented with a mixed episode, which was associated with a lower likelihood of recovery and greater use of antidepressant therapy compared to a pure manic state during follow-up (14). The Systematic Treatment Optimization Program for Early Mania (STOP-EM) project followed 53 patients presenting with a first episode of mania, and found that more than half experienced recurrence of a mood episode during the one-year follow-up, with a mean time to event of 7.9 months (15). The mean duration of mood episodes in BD I, in a longitudinal analysis of 219 patients followed for up to 25 years, was found to be 13 weeks (16).

Diagnostic assessment

The proposed fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is scheduled to be completed by mid-2013. Revisions suggested by the International Society for Bipolar Disorders Diagnostic Guidelines Task Force (17) were summarized in the previous update to these guidelines (3). DSM-5 will have separate chapters for bipolar and related conditions, and depressive disorders. The condition 'BD not otherwise specified' (NOS) has been replaced with 'bipolar conditions not elsewhere classified'. Substance-induced BD and BD associated with a general medical condition have been added.

In the criteria for a manic episode, 'abnormally and persistently increased activity or energy' has been added to criterion A, which previously referred only to a distinct period of abnormally and persistently elevated, expansive, or irritable mood. A manic episode emerging during antidepressant treatment can qualify as a manic episode of BD, provided that the symptoms persisted beyond the physiological effects of treatment. The 'mixed episode' diagnosis has been replaced with a 'mixed features' specifier, requiring three symptoms of the opposite pole, which would apply to manic, hypomanic, and depressive episodes (18). In addition, dimensional specifiers for anxiety and suicide risk have also been proposed.

Chronic disease management

BD is a chronic illness and patients require long-term multi-disciplinary management as described in the 2005 guidelines (1). A small, cluster-randomized controlled trial (RCT) examined the effect of community mental health teams (n = 23) who received enhanced training in relapse prevention

versus treatment-as-usual (TAU) in 96 patients with BD (19). The median survival time of patients treated by the trained teams was prolonged by 8.5 weeks compared to those receiving TAU (42 weeks versus 33.5 weeks). A collaborative care model including clinician support through the use of simplified guidelines was found to result in significantly greater guideline-concordant therapy over a three-year follow-up period compared to TAU in patients with BD ($n = 306$) (20).

Data suggest that use of a symptom checklist can substantially increase the recognition of early warning signs for depressive or manic relapse (21). There was a positive correlation between the frequency of monitoring and social/occupational functioning.

Psychosocial interventions

When used as adjuncts to pharmacotherapy, psychosocial interventions such as group psychoeducation, cognitive behavior therapy (CBT), and interpersonal and social rhythm therapy (IPSRT) have demonstrated significant benefits, both in the treatment of acute depressive episodes and also as long-term maintenance treatment, including decreased relapse rates, mood fluctuations, need for medications, and hospitalizations, as well as increased functioning and medication adherence (1–3). Therefore, providing psychological treatments –and, in particular, brief psychoeducation, which has been demonstrated to be as effective as CBT at much lower cost (22) – is an essential aspect of managing patients with BD.

A family-focused treatment approach designed to help caregivers improve illness management skills and their own self-care was shown to effectively reduce depressive symptoms and health-risk behavior among caregivers and family members, and reduce depressive symptoms in patients (23).

The availability of internet-based strategies has grown substantially, with demonstrated efficacy in reducing depressive symptoms and improving psychological quality of life (24–27).

Section 3. Acute management of bipolar mania

Emergency management of acute mania

The acutely manic bipolar patient may present in an agitated state that acts as a barrier to therapy, interrupts the physician–patient alliance, and creates a disruptive, even hazardous, environment. Whenever possible, oral therapy should be offered first, as evidence suggests that oral agents can be as effective as intramuscular agents (28,

29). Intramuscular injections offer an alternative when oral therapy cannot be reliably administered.

Based on current data, the oral atypical antipsychotic agents, risperidone (level 2) (29, 30), olanzapine (level 2) (30), and quetiapine (level 3) (30, 31), should be considered first in the treatment of acute agitation. In patients who refuse oral medications, intramuscular olanzapine (level 2) (32–35), ziprasidone (level 2) (35–38), and aripiprazole (level 2) (39) or a combination of intramuscular haloperidol and a benzodiazepine should be considered (level 2) (29, 35, 38, 40, 41). In general, benzodiazepines should not be used as monotherapy, but are useful adjuncts to sedate acutely agitated patients (1).

New data also support the use of intravenous sodium valproate (level 3) (42) and oral divalproex ER (level 3) (31) for rapid improvement of acute mania.

Pharmacological treatment of manic episodes

Pharmacological management of acute manic episodes should follow the algorithm outlined in Figure 3.1 (1–3). New clinical trial data, and the availability of several agents, justify some changes to the recommendations. Monotherapy with asenapine, paliperidone ER, and divalproex ER, as well as adjunctive asenapine, have been added as first-line options (Table 3.3).

Step 1. Review general principles and assess medication status: Recommendations from 2005 guidelines remain unchanged.

Step 2. First-line therapies: A comprehensive meta-analysis of 68 trials supported the efficacy of pharmacotherapy for the treatment of acute mania (43). Lithium, divalproex, risperidone ER, paliperidone ER, olanzapine, quetiapine, aripiprazole, ziprasidone, and asenapine (first line), carbamazepine, and haloperidol (second line), were significantly more effective than placebo, whereas gabapentin, lamotrigine, and topiramate were not (not recommended) (43). Haloperidol was more effective than a number of antimanic agents but not olanzapine or risperidone, both of which were more effective than valproate, ziprasidone, and lamotrigine. Two other recent meta-analyses also support the efficacy of lithium/divalproex and atypical antipsychotic agents for the treatment of acute mania (44, 45).

Lithium/divalproex. The efficacy of lithium and divalproex in the management of acute mania is

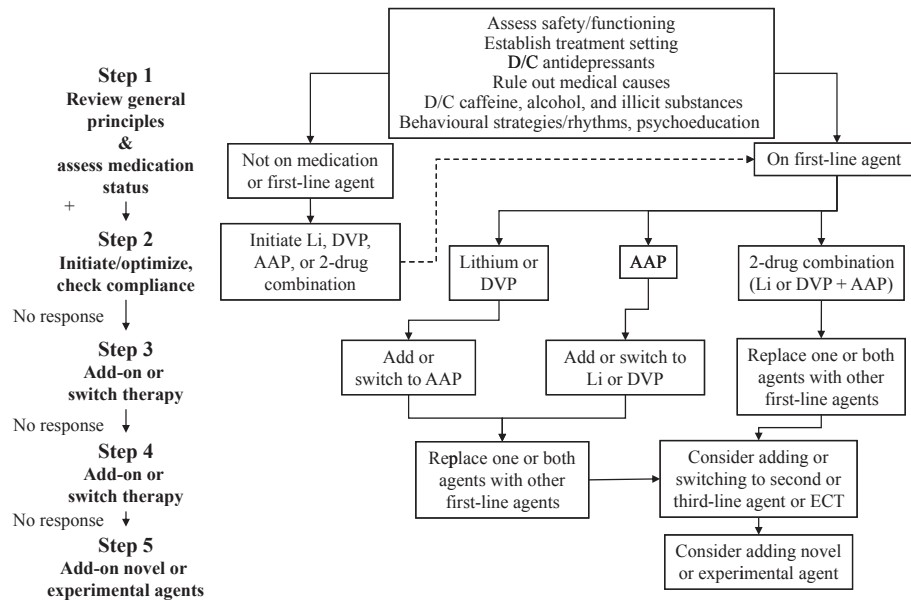


Fig. 3.1. Treatment algorithm for acute mania. Novel/experimental agents: zotepine, levetiracetam, phenytoin, mexiletine, omega-3-fatty acids, calcitonin, rapid tryptophan depletion, allopurinol, amisulpride, folic acid, memantine. D/C = discontinue; Li = lithium; DVP = divalproex; AAP = atypical antipsychotic agent.

Table 3.3. Recommendations for pharmacological treatment of acute mania

First line	<u>Monotherapy:</u> lithium, divalproex, divalproex ER^a , olanzapine ^b , risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, asenapine^a , paliperidone ER^a <u>Adjunctive therapy with lithium or divalproex:</u> risperidone, quetiapine, olanzapine, aripiprazole, asenapine^a
Second line	<u>Monotherapy:</u> carbamazepine, carbamazepine ER, ECT, haloperidol^a <u>Combination therapy:</u> lithium + divalproex
Third line	<u>Monotherapy:</u> chlorpromazine, clozapine, oxcarbazepine, tamoxifen, cariprazine^a (not yet commercially available) <u>Combination therapy:</u> lithium or divalproex + haloperidol, lithium + carbamazepine, adjunctive tamoxifen
Not recommended	<u>Monotherapy:</u> gabapentin, topiramate, lamotrigine, verapamil, tiagabine <u>Combination therapy:</u> risperidone + carbamazepine, olanzapine + carbamazepine

ECT = electroconvulsive therapy; XR or ER = extended release.

^aNew or change to recommendation.

^bGiven the metabolic side effects, use should be carefully monitored.

well established (level 1) (1–3). Two large, 12-week, open, randomized trials comparing lithium to divalproex found comparable efficacy and tolerability of these agents for the treatment of acute mania (46, 47).

A large (n = 521), 12-week RCT compared divalproex, olanzapine, and placebo in patients with mild to moderate mania. At three weeks, improvements in mania scores were significant with olanzapine versus placebo but not with divalproex versus olanzapine or placebo. After 12 weeks of treatment, improvements in both active treatment groups were significant versus placebo, but olanzapine was significantly more efficacious than divalproex (48).

The results of two three-week RCTs assessing the efficacy of the ER formulation of divalproex for the treatment of acute mania have now been published (49, 50). One study demonstrated statistically significant improvements in manic symptoms compared to placebo (level 2) (49), while the other did not (50). In the first, Bowden et al. (49) found significantly greater improvement in manic symptoms and higher response rates (48% versus 34%, $p = 0.012$) with divalproex ER versus placebo, while Hirschfeld et al. (50) found no statistically significant difference in mania scores with divalproex ER versus placebo; however, discontinuation rates were over 80% and dosing may have been lower than optimal.

Given the level 1 evidence to support the immediate-release formulation of divalproex, as well as the high discontinuation rate and dosing issues in the negative trial, divalproex ER has been added as a first-line therapy, although, if prescribed, attention should be paid to dosing and serum levels.

Atypical antipsychotic monotherapy. Substantial RCT data support the efficacy of atypical antipsychotic monotherapy with olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole for the first-line treatment of acute mania (level 1) (1–3).

As reviewed earlier, a large ($n = 521$), 12-week RCT comparing divalproex, olanzapine, and placebo in patients with mild to moderate mania found that improvements in mania scores with olanzapine were significantly greater than with placebo after three weeks, and greater than with both divalproex and placebo after 12 weeks (48).

In a meta-analysis of six aripiprazole monotherapy RCTs in acute mania involving 2303 patients, the effect size was 0.34 versus placebo at week three, with a response generally being seen at day three (level 1) (51). A 12-week RCT of aripiprazole monotherapy in acute mania found significantly greater improvements in the Young Mania Rating Scale (YMRS) scores at week three with aripiprazole (-12.0 , $p < 0.05$) or haloperidol (-12.8 , $p < 0.01$) compared to placebo (-9.7), which were maintained to week 12; haloperidol was included as an active control and was not statistically compared to aripiprazole (52).

Additional data are also available comparing ziprasidone to placebo and haloperidol in a 12-week RCT. Improvements in mania scores and response rates at week three were significantly greater than with placebo for both active treatments, but haloperidol was significantly more effective than ziprasidone. During the nine-week extension phase, responses were maintained for the majority of patients receiving active treatments. Ziprasidone showed a superior tolerability profile and lower discontinuation rates during the extension phase (53).

Two three-week, double-blind RCTs demonstrating the efficacy of paliperidone ER in patients with manic or mixed episodes, which were previously cited in abstract form, have now been published (level 1) (54, 55). Paliperidone ER has been upgraded to a first-line option.

Two three-week, double-blind RCTs demonstrating the efficacy of asenapine as monotherapy for acute mania (56, 57), as well as nine-week and 40-week extension phase results demonstrating the

maintenance of benefits (58, 59), which were previously cited in abstract form, have now been published (level 1). Asenapine has been upgraded to a first-line option.

Atypical antipsychotic combination therapy. As previously reported, a six-week, placebo-controlled RCT showed that adding aripiprazole to lithium or divalproex in 384 patients with an inadequate response was significantly more effective than placebo from week 1 onward (60). A 46-week open-label extension of this study found that aripiprazole as an adjunct to lithium or divalproex provided continued improvement in mania but not depression (61).

A 12-week RCT demonstrating significant improvements in mania symptoms with adjunctive asenapine added to lithium/divalproex compared to placebo that was previously cited in abstract form has still not been published, but 40-week extension results have now been reported (level 2) (62). Of the original 318 patients, 71 completed the 40-week extension; there were additional improvements in mania scores at 52 weeks in both the asenapine and placebo groups. Adjunctive asenapine has been moved to a first-line option.

Step 3. Add-on or switch therapy (alternate first-line therapies): No changes from 2005 guidelines.

Step 4. Add-on or switch therapy (second- and third-line therapies):

Second-line options. A small RCT in 44 patients with manic, mixed, or depressive episodes found that among patients who were on, or thought to benefit from, carbamazepine, there were no differences in mood ratings or in the total level of adverse events with immediate-release versus ER carbamazepine (63, 64). However, there were significantly fewer autonomic and gastrointestinal adverse events with carbamazepine ER (64).

While electroconvulsive therapy (ECT) can be an effective option, research studies have not been rigorous and therefore it continues to be recommended as a second-line therapy (level 3) (1). In an RCT of ECT as adjunct to antipsychotic therapy, bilateral, twice-weekly ECT delivered at stimulus intensities just above seizure threshold was as effective and safe as ECT administered at stimulus intensities 2.5 times the seizure threshold in rapidly resolving the symptoms of acute mania (65).

In a meta-analysis of 13 haloperidol-controlled trials, the drug was significantly more effective than lithium, divalproex, quetiapine, aripiprazole,

ziprasidone, carbamazepine, asenapine, and lamotrigine (43). Given the strong data for efficacy, haloperidol has been upgraded to a second-line option. However, haloperidol should only be used on a short-term basis to treat acute mania as continuation of haloperidol may increase the risk of a depressive episode (43).

Third-line options. A small ($n = 60$), 12-week RCT comparing oxcarbazepine to divalproex in patients with acute mania found no significant differences in improvements in mania scores or remission rates between the two treatments, but divalproex was associated with more adverse events (66). In another small ($n = 52$) RCT, adjunctive oxcarbazepine was more effective than carbamazepine as add-on therapy in patients who had previously been inadequate responders to lithium, although both agents improved manic and depressive scores versus baseline (67). As described in the previous updates to these guidelines, there are other small positive trials, but there is also a negative placebo-controlled RCT, and these new trials are small and do not include a placebo control arm; therefore, oxcarbazepine remains as a third-line option.

Cariprazine, a new dopamine D3/D2 receptor antagonist, appears promising for the treatment of acute mania, but has not yet been approved by Canadian or US regulatory agencies. The results of a three-week, phase 2, RCT, presented in abstract form, reported significant reductions in mania scores with cariprazine compared to placebo (level 2) (68).

Step 5. Add-on novel or experimental agents:

Zotepine is an antipsychotic agent that has been approved in some European countries and in Japan for the treatment of schizophrenia. In a four-week, single-blind trial, adjunctive zotepine added to lithium or divalproex therapy in 45 inpatients with moderate-to-severe mania was as effective as adjunctive haloperidol in improving mania scores (69).

Two RCTs have now demonstrated the efficacy of adjunctive allopurinol for the treatment of acute mania (level 1) (70, 71). In an eight-week RCT, allopurinol as adjunct to lithium plus haloperidol was found to be significantly more effective than placebo in 82 patients hospitalized with acute mania (70). In the second RCT ($n = 180$), comparing the addition of allopurinol, dipyridamole, or placebo to lithium for four weeks, allopurinol led to significantly greater improvements in mania scores and remission rates versus placebo (71). Although there is level 1 evidence for the use of

allopurinol, given that it can cause hepatomegaly as well as hypersensitivity reactions such as Steven–Johnson syndrome and toxic epidermal necrolysis, it is recommended only for those patients that are refractory to other first-, second, and third-line treatments.

Preliminary evidence previously suggested antimanic efficacy associated with tamoxifen (1). A six-week, placebo-controlled RCT has now demonstrated significantly greater improvements in mania scores with tamoxifen as an adjunct to lithium in 40 inpatients with acute mania compared to lithium alone (level 2) (72).

In a three-week RCT in 88 acutely manic patients on divalproex, adjunctive folic acid was significantly better than placebo in improving mania scores (level 2) (73).

A three-week, open-label, pilot trial in 33 patients with manic or mixed episode BD I found that 30–50% of patients responded to doses of memantine ranging from 20 mg to 40 mg (level 3) (74).

Given the limited data, at this time, these agents can only be recommended as add-on therapies after failure of standard therapies.

Adjunctive therapies with negative data requiring further study:

A six-week RCT that found no significant improvements in manic symptoms with adjunctive flexible-dose paliperidone in patients with manic or mixed episodes who had not responded to lithium or divalproex, was previously cited in abstract form and has now been published (level 2, negative) (75). Given that paliperidone monotherapy is effective, and that lithium or valproate does not affect the metabolism of paliperidone, the lack of efficacy of combination therapy is surprising. In spite of the fact that it was a flexible-dose trial, paliperidone ER may have been under-dosed, since the monotherapy studies suggest that 12 mg/day is the most effective dose and the mean dose used was 8.1 (3.30) mg/day, with 45% of the patients receiving a final dose of 6 mg/day in this trial. In addition, a post-hoc subgroup analysis found that adjunctive paliperidone ER was superior to lithium or divalproex monotherapy for patients diagnosed with a manic episode ($p = 0.020$).

A three-week RCT in over 600 patients with BD mania/mixed episodes found no significant benefits with adjunctive ziprasidone at either high (120–160 mg/day) or low (40–80 mg/day) doses compared to placebo (76). The trial has not yet been published, but the results are available at <http://www.clinicaltrials.gov>.

In light of these negative trials, adjunctive use of paliperidone ER or ziprasidone, at the dosages

used by the above-noted studies, is not recommended.

Mania with psychotic features

A meta-analysis of four RCTs of aripiprazole supports its antipsychotic effects, as measured by the Positive and Negative Syndrome Scale (PANSS) score, during the acute manic and maintenance phases of BD (77). The effect sizes for aripiprazole versus placebo were highest for the PANSS-positive subscale (0.28) and the PANSS-hostility subscale (0.24).

Mixed states

A six-week RCT ($n = 202$) evaluating adjunctive olanzapine compared to adjunctive placebo demonstrated significantly greater and earlier reductions in manic and depressive symptoms in patients with mixed episodes inadequately controlled with divalproex (78). Post-hoc analysis of this study found that response (Clinical Global Impression–Severity decrease ≥ 1) at day two was predictive of mixed symptom remission (79).

A post-hoc analysis of two asenapine RCTs in patients with manic or mixed episodes demonstrated statistically significant decreases in depres-

sion scores with asenapine versus placebo in patients with severe baseline depressive symptoms ($n = 604$); differences between the active comparator olanzapine and placebo were not significant, which makes the interpretation of these results more difficult as it raises the possibility of a negative study (80).

Section 4. Acute management of bipolar depression

Pharmacological treatment of depressive episodes

Pharmacological management of acute bipolar depressive episodes should follow the algorithm outlined in Figure 4.1 (1–3). The recommendations for first- and second-line therapies are largely unchanged, except for the addition of lurasidone monotherapy and lurasidone or lamotrigine plus lithium or divalproex as second-line options. Based on negative data, ziprasidone alone or as adjunctive therapy, and adjunctive levetiracetam have been added as not-recommended options for the treatment of bipolar depression (Table 4.3).

Several meta-analyses have assessed the efficacy of atypical antipsychotic agents and other medications for the treatment of bipolar depression (81, 82). A meta-analysis of atypical antipsychotic agents for bipolar depression included five trials (two monotherapy trials with each of quetiapine

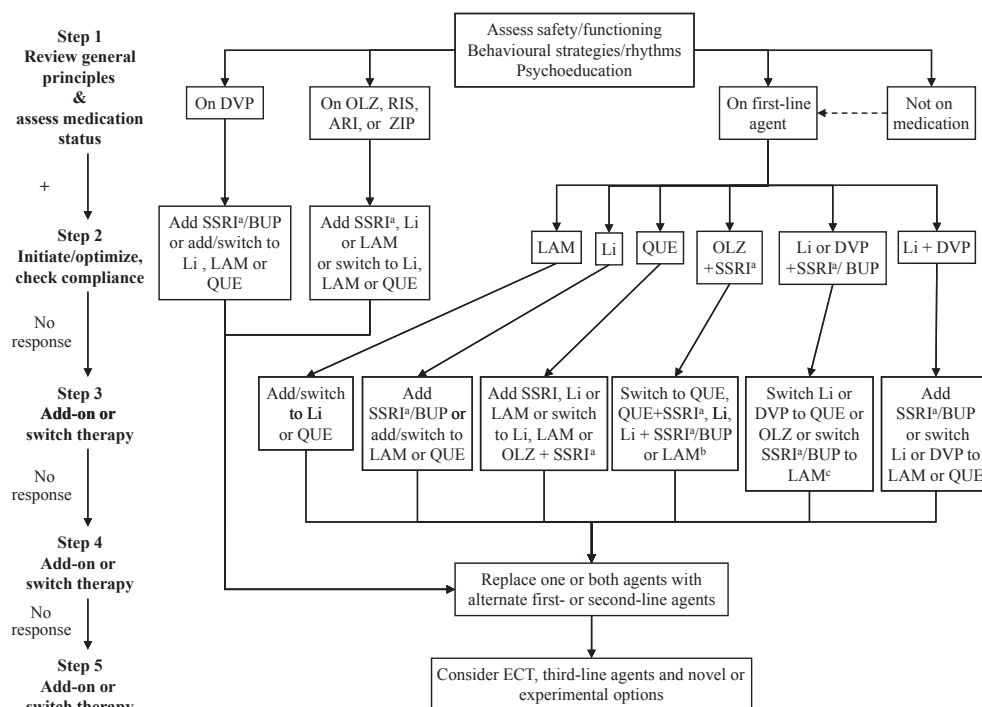


Fig. 4.1. Treatment algorithm for the management of bipolar I depression. Novel/experimental agents: adjunctive pramipexole, eicosapentaenoic acid (EPA), riluzole, topiramate, N-acetyl cysteine (NAC), ketamine, armodafinil, and chronotherapy. DVP = divalproex; OLZ = olanzapine; RIS = risperidone; ARI = aripiprazole; ZIP = ziprasidone; SSRI = selective serotonin reuptake inhibitor; BUP = bupropion; Li = lithium; LAM = lamotrigine; QUE = quetiapine; ECT = electroconvulsive therapy. ^aExcept paroxetine. ^bOr switch the SSRI to another SSRI. ^cOr switch the SSRI or BUP to another SSRI or BUP.

Table 4.3. Recommendations for pharmacological treatment of acute bipolar I depression^a

First line	<u>Monotherapy</u> : lithium, lamotrigine, quetiapine, quetiapine XR <u>Combination therapy</u> : lithium or divalproex + SSRI ^b , olanzapine + SSRI ^b , lithium + divalproex, lithium or divalproex + bupropion
Second line	<u>Monotherapy</u> : divalproex, <i>lurasidone</i>^c <u>Combination therapy</u> : quetiapine + SSRI ^b , adjunctive modafinil, <i>lithium or divalproex + lamotrigine</i>^c , <i>lithium or divalproex + lurasidone</i>^c
Third line	<u>Monotherapy</u> : carbamazepine, olanzapine, <i>ECT</i>^d <u>Combination therapy</u> : lithium + carbamazepine, lithium + pramipexole, lithium or divalproex + venlafaxine, lithium + MAOI, lithium or divalproex or AAP + TCA, lithium or divalproex or carbamazepine + SSRI ^b + lamotrigine, <i>quetiapine + lamotrigine</i>^c
Not recommended	<u>Monotherapy</u> : gabapentin, aripiprazole, <i>ziprasidone</i>^c <u>Combination therapy</u> : <i>adjunctive ziprasidone</i>^c , <i>adjunctive levetiracetam</i>^c

AAP = atypical antipsychotic agent; ECT = electroconvulsive therapy; MAOI = monoamine oxidase inhibitor; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; XR = extended release.

^aThe management of a bipolar depressive episode with antidepressants remains complex. The clinician must balance the desired effect of remission with the undesired effect of switching. See detailed discussion in *Clinical questions and controversies* section.

^bExcept paroxetine.

^c***New or change to recommendation.***

^dCould be used as first- or second-line treatment in certain situations (see text).

and aripiprazole, and one combination trial with olanzapine) and found significantly greater improvement compared to placebo for weeks 1–6 but not for weeks seven and eight (primarily accounted for by a tapering of effect in aripiprazole studies) (81). This suggests that the efficacy of these agents is not a class effect and that individual agents may show differential benefits, and, as such, generalizations on the role of atypical antipsychotic agents for depressive symptoms cannot be made. Another meta-analysis included 19 trials assessing mainly quetiapine (five trials) and lamotrigine (six trials), but also paroxetine, lithium, olanzapine, aripiprazole, phenelzine, and divalproex for the treatment of bipolar depression (82). This analysis found the highest reductions in Montgomery–Åsberg Depression Rating Scale (MADRS) scores with the olanzapine plus fluoxetine combination and quetiapine monotherapy compared to placebo. In this analysis, lamotrigine, paroxetine, aripiprazole, and lithium were not significantly different from placebo in improving depression scores. However, as cited in previous iterations, a meta-analysis of individual patient data supported the efficacy of lamotrigine monotherapy (83).

Step 1. Review general principles and assess medication status: Recommendations from 2005 guidelines remain unchanged.

Step 2. Initiate or optimize therapy and check adherence (first-line therapies): Lithium, lamotrigine, quetiapine, and quetiapine extended release (XR)

monotherapies, as well as lithium or divalproex plus selective serotonin reuptake inhibitor (SSRI), olanzapine plus SSRI, lithium plus divalproex, and lithium or divalproex plus bupropion all continue to be recommended as first-line choices for bipolar depression.

Data suggest that the absence of early improvement (2–3 weeks) may be a highly reliable predictor of eventual non-response, suggesting that these patients may benefit from a change in therapy (84, 85).

Lithium. The early results of the National Institute of Mental Health (NIMH) lithium treatment moderate dose use study have been presented (86). This pragmatic study randomized 283 patients with BD I or BD II to receive six months of open-label ‘moderate dose’ (600 mg/day) lithium plus optimized treatment [per Texas Medication Algorithms (87)] versus optimized treatment alone and found no significant differences between treatment groups. However, given that this was an open-label study, and in the absence of further study details, recommendations for adjunctive lithium use remain unchanged.

Quetiapine monotherapy. The four large published RCTs demonstrating the efficacy of quetiapine monotherapy in bipolar depression, which were cited in previous iterations of these guidelines, have now all been published: BipOLar DEpResion (BOLDER) I (88) and II (89) and Efficacy of Monotherapy SEROQUEL in BipOLar DEpres-

sioN (EMBOLDEN) I (90) and EMBOLDEN II (91) (level 1).

The eight-week RCT demonstrating significantly greater improvement in depressive symptoms with quetiapine XR monotherapy in patients with BD I or BD II depression, which was previously cited, has now been published (92).

Olanzapine + fluoxetine. There are level 1 data demonstrating the efficacy of olanzapine–fluoxetine combination (OFC) therapy for the treatment of BD I depression (1–3). Follow-up results from a previously described RCT [seven-week outcome data (93)] found significantly greater improvements in depressive and manic symptoms with OFC versus lamotrigine in 410 patients with BD I at study end (94). However, OFC treatment was associated with a significantly increased risk of treatment-emergent hypercholesterolemia and weight gain. In addition, a post-hoc analysis of a previously cited combination study (95) found that both OFC and olanzapine monotherapy were more efficacious than placebo in patients with BD I mixed depression (i.e., syndromal depression and subsyndromal mania/hypomania).

Step 3. Add-on or switch therapy (alternate first- or second-line therapies):

Second-line options

Divalproex monotherapy. Four small RCTs have assessed the efficacy of divalproex or divalproex ER for the treatment of BD I or BD II depression (level 1) (96, 97). Two meta-analyses of these trials (total $n = 142$), by separate groups, concluded that divalproex was more effective than placebo for the treatment of bipolar depression, but the strength of the conclusions was limited by sample size (96, 97). Therefore, given the limited evidence, divalproex continues to be recommended as a second-line option.

Lurasidone. Two six-week RCTs have demonstrated the efficacy of lurasidone as monotherapy (98) or as an adjunct (99) in patients with bipolar depression. Lurasidone monotherapy significantly reduced depressive symptoms in patients with BD I depression as early as week two compared to placebo (level 2) (98). Similarly, when used as an adjunct to lithium or divalproex, lurasidone significantly reduced depressive symptoms, and improved functioning and quality of life compared to placebo in patients with BD I depression who had an inadequate response to lithium or divalproex alone (level 2) (99). These data look very promising and if clinical experience supports effi-

cacy, lurasidone will be upgraded to one of the first-line treatments in the next revision.

Lamotrigine + lithium or divalproex. In an eight-week RCT, the acute effect of lamotrigine was greater than that of placebo as an add-on to lithium for BD I or BD II depression ($n = 124$) (100). Non-responders in this trial entered a second phase in which paroxetine was added; this addition showed benefit in non-responders to lithium + placebo, but not in non-responders to lithium + lamotrigine (101). Given the slow titration required for lamotrigine, this treatment is recommended either in monotherapy or as an add-on therapy primarily for those with mild-to-moderate bipolar depression, and in particular for those with depression recurrences, given its efficacy in preventing depressive relapses.

Step 4. Add-on or switch therapy (alternate first- or second-line therapies): No changes from 2005 guideline (1).

Step 5. Add-on or switch therapy (third-line agents and novel/experimental therapies):

Third-line options

Olanzapine monotherapy. There are now two large RCTs demonstrating the efficacy of olanzapine monotherapy for the treatment of bipolar depression (level 1) (95, 102). In the earlier of these two trials, olanzapine monotherapy demonstrated a statistically significant, but clinically modest antidepressant effect in a large ($n = 833$), eight-week RCT in patients with bipolar depression (95), and was recommended as a third-line option (1).

In the subsequent large RCT, available in abstract form, 514 patients with bipolar depression achieved significantly greater improvement in depressive symptoms with olanzapine compared to placebo (MADRS -13.8 versus -11.7 , $p = 0.018$) over six weeks of treatment (102). However, olanzapine was also associated with significantly greater rates of metabolic changes (102). A small ($n = 20$), open-label study provided additional support for the efficacy of olanzapine monotherapy in patients with BD I or BD II depression (103).

Although there is level 1 evidence, the magnitude of benefit of olanzapine monotherapy was only modestly greater than that of placebo (95, 102). In the earlier trial (95), the increased efficacy of olanzapine relative to placebo was mainly accounted for by changes in sleep, appetite, and inner tension, which are not the core symptoms of depression (81). In addition, as adverse events were

marked in the recent trial (102), this strategy continues to be recommended as a third-line option.

Quetiapine + lamotrigine. A small, open trial in 39 patients with BD I and BD II found that the combination of lamotrigine plus quetiapine was beneficial in treatment-resistant bipolar depression (level 3) (104).

Carbamazepine. There is additional evidence to support the use of carbamazepine (level 2), as a small RCT in a mixed population of 44 patients with BD found that ER carbamazepine was as effective as the immediate-release form, with fewer autonomic and gastrointestinal adverse events (63, 64).

ECT. As stated in previous iterations of the guidelines, the use of ECT should be considered earlier in patients who have psychotic bipolar depression, in those at high risk for suicide, and in those with significant medical complications due to not drinking and eating. Clinical experience and open-label data continue to accumulate and support the efficacy of ECT. In an open trial, similar rates of response and remission were observed in patients with bipolar depression (70% and 26%, respectively) and those with mixed states (66% and 30%, respectively) (105). A retrospective analysis of 201 patients with BD receiving ECT concluded that those receiving concomitant anticonvulsants achieved comparable symptomatic improvement to those not on anticonvulsants; however, they required a significantly greater number of ECT sessions to achieve this (106). Two RCTs comparing different ECT protocols found no difference in response rates in patients with bipolar or unipolar depression (107, 108).

Novel or experimental agents

Data were previously described demonstrating the benefits of adjunctive use of the following agents: pramipexole (level 2), eicosapentaenoic acid (EPA) (level 2), riluzole (level 3), topiramate (level 3), and N-acetyl cysteine (NAC) (level 2) (1–3).

Additional open-label data support the use of adjunctive riluzole and adjunctive NAC (109, 110). Patients in a small, open-label, imaging study reported improvements in depressive symptoms with riluzole (level 3) (109), while data from a large (n = 149), eight-week, open-label trial found significant improvement in depressive symptoms with adjunctive NAC in patients with BD I, II, or NOS depression (110).

Preliminary data are also available to support other novel treatments not previously investigated

in patients with bipolar depression, including adjunctive ketamine, armodafinil, and chronotherapy. A two-week, crossover RCT assessing adjunctive ketamine infusion in patients with treatment-resistant bipolar depression identified a robust early antidepressant effect (within 40 min), with improvement remaining significant versus placebo through day three (level 2) (111). An eight-week RCT in 257 patients with BD I depression reported a trend toward greater improvement in depressive symptoms with adjunctive armodafinil versus placebo on some, but not all depression symptom scales (level 2) (112). Adjunctive combined chronotherapy (sleep deprivation, exposure to bright light, and sleep-phase advance) demonstrated a more rapid and sustained antidepressant response compared to medication alone (lithium + antidepressant) in a seven-week RCT in 49 patients with bipolar depression (level 3) (113). Patients receiving adjunctive chronotherapy experienced a significantly greater reduction in depressive symptoms within 48 hours, which was sustained throughout the seven weeks.

Not recommended for the treatment of acute bipolar depression:

Ziprasidone monotherapy. Data are now available from two negative RCTs of ziprasidone monotherapy in BD I depression (level 1, negative) (114, 115). The trials have not yet been published, but results are available at <http://www.clinicaltrials.gov> (114, 115). Both were large trials (n = 381 and n = 504, respectively) in patients with BD I depression, and both demonstrated no significant improvements in depression scores compared to placebo. While ziprasidone is not recommended for bipolar depression, patients who are using ziprasidone with benefit (initiated during mania) do not need to have it discontinued.

Adjunctive therapies with negative data requiring further study:

Adjunctive ziprasidone. A large RCT assessing adjunctive ziprasidone (mean dose 90 mg) added to therapy with lithium, divalproex, or lamotrigine in 298 patients with BD I depression found no significant difference between active treatment and placebo (level 2, negative) (116).

Adjunctive aripiprazole. While open-label trials suggest a benefit of adjunctive aripiprazole for the treatment of bipolar depression (level 3) (117, 118), a small RCT did not find a significant effect compared to placebo (level 2, negative) (119). In a six-week RCT, 23 inpatients with bipolar depres-

sion on lithium or divalproex were given open-label citalopram, and randomized to adjunctive aripiprazole or placebo. Depressive symptoms improved, with no significant differences between treatment groups (level 2 negative) (119).

In a 16-week, prospective, open-label trial, aripiprazole (add-on or monotherapy) was associated with a significant decline in depressive symptoms over 16 weeks among 85 patients with bipolar depression who were unresponsive to other medications (lithium, anticonvulsants, or antipsychotic agents) (level 3) (117). There was also a significant reduction in self-rated anhedonia among patients with BD I depression treated with aripiprazole in the same study (120). Another small ($n = 20$), six-week, open-label trial demonstrated improvement in depressive symptoms, with a 44% response rate with aripiprazole as add-on or monotherapy for BD I, II, or NOS depression (level 3) (118).

Adjunctive levetiracetam. A six-week RCT in 32 patients with bipolar depression found no significant differences in the change in depression scores with adjunctive levetiracetam versus placebo (level 2, negative) (121).

Clinical questions and controversies

What is the role of antidepressants in patients with bipolar depression?

The role of antidepressants in patients with bipolar depression remains one of the most controversial areas in psychiatry. Antidepressants are the most commonly used treatments for bipolar depression (122, 123) as clinicians continue to believe that, based on their clinical experience, these are effective for bipolar depression. However, the limited, but growing body of clinical trial data has not been consistent in supporting their role. For instance, OFC was shown to be more effective than placebo or olanzapine monotherapy (93, 95), but the combination of paroxetine or bupropion with a *mood stabilizer* was not more effective than a *mood stabilizer* plus placebo (124). However, this study had severe methodological limitations; most patients were also participating in a psychotherapy trial, and an unknown proportion of patients continued to use the previous antidepressant they had been on at baseline. In another study, paroxetine monotherapy (20 mg/day) was not superior to placebo in improving bipolar depressive symptoms (125). It is unknown if higher doses of paroxetine would have been more effective.

Although individual studies are contradictory, the most recent meta-analysis, which included 15

RCTs (126), found a strong trend for superiority of antidepressants over placebo for the acute treatment of bipolar depression ($p = 0.06$). Antidepressants were not associated with a significantly increased risk of manic switch (126). Most negative studies of antidepressants for bipolar depression to date have employed paroxetine as the antidepressant (91, 125, 127). A meta-analysis of the efficacy of antidepressants in unipolar depression (128) suggested that clinically important differences exist between various antidepressants in terms of efficacy and acceptability. Interestingly, paroxetine was inferior to a number of other antidepressants in this meta-analysis. The risk of manic/hypomanic switch does not appear to be a major concern with modern antidepressants when used in conjunction with a 'mood stabilizer' or an atypical antipsychotic agent, at least during short-term treatment; therefore, safety does not appear to be a significant issue during the acute treatment of bipolar depression. An important caveat is that the current definition of switch requires threshold mania; milder switches, which are common, are not captured by the default definition (129). Similarly, the metrics of cycle acceleration are not captured in current definitions or trial designs (130).

Given the above, we believe that the following conclusions and recommendations are warranted regarding the use of antidepressants for bipolar depression: (i) SSRIs (other than paroxetine) and bupropion could be used as first-line treatments in conjunction with a *mood stabilizer* for acute short-term treatment of bipolar depression, with the objective of tapering and discontinuing antidepressants 6–8 weeks after full remission of depression; (ii) avoid the use of tricyclic antidepressants and venlafaxine (131, 132) as they are associated with an increased risk of manic switch; (iii) antidepressants should not be used to treat a current mixed episode or in patients with a history of rapid cycling; (iv) monotherapy with antidepressants is **not** recommended for bipolar depression.

Section 5. Maintenance therapy for bipolar disorder

Adherence

New data provide further insight into adherence to maintenance therapy in patients with BD. In several analyses, adherence was positively associated with higher satisfaction with medication, monotherapy, a college degree, and fear of relapse, and was negatively associated with illness factors (substance use, previous hospitalization, psychotic symptoms, reduced insight into illness), medication factors (side effects, no perceived daily benefit,

difficulties with medication routines), and patient attitudes (belief that medications are unnecessary, negative attitudes toward medications, perceived change in appearance, perceived interference with life goals) (133–139). Under-dosing can also lead to higher discontinuation rates; patients receiving lower doses of ziprasidone had significantly higher discontinuation rates than those receiving medium or high doses (140).

Non-adherence has been linked to a high frequency of episodes (particularly depressive episodes), a higher risk of hospitalization and emergency room visits, as well as higher employee costs of absenteeism, short-term disability, and workers' compensation (137, 141–144). In an analysis involving UK data, the direct costs of care were two to three times higher in patients who relapsed compared to those who did not over the 6–12-month follow-up (145).

Predictors of recurrence

In observational studies, predictors of symptomatic remission and recovery during 1–2 years of follow-up in patients with manic episodes included: Caucasian ethnicity, a previous manic episode, good social functioning (no work or social impairment, living independently or with family), outpatient treatment, and being neither satisfied nor dissatisfied with life (146, 147).

In patients with rapid cycling treated with lithium or divalproex, increased risk for non-stabilization was associated with a history of recent substance use disorder (SUD), early-life verbal abuse, female gender, and late onset of first depressive episode (148). Among responders to long-term lithium therapy, the risk of recurrence was higher in those with atypical features (mainly mood-incongruent psychotic symptoms), inter-episodic residual symptomatology, and rapid cycling (149).

Psychosocial interventions for maintenance therapy

As reported in previous iterations of these guidelines, data have supported the benefits of adjunctive psychoeducation, CBT, family therapy, and IPSRT in reducing recurrences and improving symptoms in patients with BD (1–3). However, recent meta-analyses assessing the efficacy of psychotherapies for patients with BD have reached discordant conclusions. One meta-analysis of four RCTs concluded that CBT had a small effect size for depressive symptoms compared to treatment as usual or wait-list controls (150). A second analysis included 12 trials and found low to medium effect sizes associated with adjunctive CBT at the end of

treatment and at follow-up (151). Another meta-analysis concluded that CBT was likely not an effective treatment strategy for the prevention of relapse in BD (152).

Given the transient benefit of CBT in the first major study of this strategy in patients with BD (153) and the negative results of a large RCT (154), the true benefit of CBT is unclear, beyond its common core element of psychoeducation (155). However, two new RCTs provide some promise. In one study comparing a group CBT intervention to treatment as usual in 50 patients, group CBT was associated with a longer median time to relapse, but no differences in time to recurrence or number of episodes (156). In a 14-week study comparing the CBT ($n = 27$) and control pharmacotherapy ($n = 14$) groups, there was a slight, although non-significant, reduction in depressive symptoms in the CBT group (157). Both of these small studies demonstrated the feasibility of group CBT rather than its efficacy, and proper replication is needed. In addition, a previously reported RCT ($n = 204$) (22), which has now been published, compared six sessions of group psychoeducation to 20 sessions of individual CBT. Both treatments demonstrated a significant benefit in terms of mood stability and reduction of recurrence, but there were no differences between the two treatments. Since the psychoeducation treatment was designed to be delivered by psychiatric nurses and was documented to be much less expensive than individual CBT, the study suggested that group psychoeducation should be prioritized as a first *universal* psychosocial treatment for BD.

RCTs of adjunctive group psychoeducation programs demonstrated a longer time to recurrence, fewer recurrences of any type, less time acutely ill, and fewer days of hospitalization during 1–5 years of follow-up (158, 159). A 12-week dyadic (patient–companion) group-based psychoeducation program demonstrated significantly lower relapse rates and a longer time to relapse compared to treatment as usual during a 60-week follow-up (160).

Pharmacological treatments for maintenance therapy

As discussed in previous guideline iterations, almost all modern maintenance studies have used an enriched design. The only exceptions are some of the older maintenance studies with lithium, which showed the efficacy of lithium for maintenance treatment in non-enriched samples. Given the efficacy of various treatments with enriched design studies, it makes intuitive sense that, in general, the treatment that worked during the acute phase is

Table 5.5. Recommendations for maintenance pharmacotherapy of bipolar disorder

First line	<u>Monotherapy</u> : lithium, lamotrigine (limited efficacy in preventing mania), divalproex, olanzapine ^a , quetiapine, risperidone LAI ^b , aripiprazole ^b <u>Adjunctive therapy with lithium or divalproex</u> : quetiapine, risperidone LAI ^b , aripiprazole ^b , ziprasidone ^b
Second line	<u>Monotherapy</u> : carbamazepine, paliperidone ER^c <u>Combination therapy</u> : lithium + divalproex, lithium + carbamazepine, lithium or divalproex + olanzapine, lithium + risperidone, lithium + lamotrigine, olanzapine + fluoxetine
Third line	<u>Monotherapy</u> : asenapine^c <u>Adjunctive therapy</u> : phenytoin, clozapine, ECT, topiramate, omega-3-fatty acids, oxcarbazepine, gabapentin, asenapine^c
Not recommended	<u>Monotherapy</u> : gabapentin, topiramate, or antidepressants <u>Adjunctive therapy</u> : flupenthixol

LAI = long-acting injection; ER = extended release; ECT = electroconvulsive therapy.

^aGiven the metabolic side effects, use should be carefully monitored.

^bMainly for the prevention of mania.

^c**New or change to recommendation.**

likely to be effective in the maintenance phase [please see the original 2005 guidelines: *Section 5. Maintenance therapy for bipolar disorder: General principles* (1)]. Based on new evidence, asenapine alone and as adjunctive therapy have been added as third-line options (Table 5.5) (1–3).

First-line options: Lithium, divalproex, olanzapine, and quetiapine (for both depression and mania), as well as lamotrigine (primarily for preventing depression), risperidone long-acting injection (LAI) and ziprasidone (primarily for preventing mania) continue to be first-line monotherapy options for maintenance treatment of BD (1–3). Quetiapine, risperidone LAI (mania), aripiprazole (mania), and ziprasidone (mania) are also recommended as adjunctive therapy with lithium or divalproex.

A systematic review of pharmacological interventions for the prevention of relapse in BD included 34 RCTs and quasi-RCTs, and concluded that lithium, olanzapine, and aripiprazole had significant effects in the prevention of manic relapses, as did divalproex, lamotrigine, and imipramine in the prevention of depressive symptoms (161). A meta-analysis of 20 RCTs (n = 5364) assessing the relative risk for relapse in patients with BD in remission confirmed the efficacy of lithium, divalproex, lamotrigine, and a number of atypical antipsychotic agents in preventing relapse to any episode versus placebo (162).

Lithium/divalproex. The Bipolar Affective disorder Lithium/ANti-Convulsant Evaluation (BALANCE) study randomized 330 patients with BD to open-label lithium monotherapy, divalproex monotherapy, or the combination after an active run-in period on the combination (163). Both the

combination and lithium monotherapy were significantly more effective than divalproex monotherapy in preventing relapse during up to two years of follow-up. Combination therapy was not significantly more effective than lithium alone. This study, however, had a number of methodological limitations, including an open design; hence, these findings need to be confirmed in double-blind trials before firm conclusions can be drawn.

Lamotrigine. During a one-year extension phase of an RCT, median time to relapse or recurrence was longer among responders receiving lamotrigine compared to those receiving placebo as an add-on to lithium ± paroxetine (ten versus 3.5 months) (164).

An open, randomized trial in patients with BD I found no differences in maintenance effectiveness between lithium (n = 78) and lamotrigine (n = 77) (165). Among patients followed for at least five years, practically no patients were maintained successfully on monotherapy with either drug.

Olanzapine. A meta-analysis of five RCTs found that olanzapine as monotherapy or an adjunct to lithium or divalproex was more effective than adjunct placebo in preventing a manic, but not any type of depressive, episode (166). The analysis concluded that olanzapine may prevent manic episodes only in patients who have responded to olanzapine for an acute episode and who have not previously had a satisfactory response to lithium or valproate.

In two recent RCTs, olanzapine was included as an active control arm, and in the continuation phase demonstrated a significantly longer time to recurrence than either risperidone LAI (167) or paliperidone ER (168).

A large, observational study (EMBLEM) included 1076 patients in a comparison of olanzapine monotherapy or as an adjunct and found no significant difference in rates of improvement, remission, or recovery, but significantly lower relapse rates with olanzapine alone compared to adjunctive olanzapine ($p = 0.01$) over the two-year follow-up (169).

Quetiapine. Three of the five large RCTs described in the 2009 guidelines (3), which demonstrated the efficacy of quetiapine alone or in combination with lithium/divalproex for maintenance therapy in BD, have now been published (level 1) (170–172). The eight-week acute-phase results of the EM-BOLDEN I (90) and II (91) trials have also been published but the long-term data remain available only in abstract form.

Risperidone LAI. Risperidone LAI monotherapy (level 2) (173) and adjunct (level 2) (174) were previously recommended as first-line maintenance therapies (3), based on RCTs presented in abstract form that have now been published. An additional 18-month continuation study has now provided level 1 evidence for maintenance risperidone LAI. Time to recurrence of any mood episode was significantly longer with risperidone LAI compared to placebo (level 1) (168). However, risperidone LAI was less effective in preventing relapse compared to olanzapine.

In addition, a small ($n = 29$), long-term, open trial demonstrated improvements in treatment adherence, reductions in any relapse rates, and reductions in re-hospitalization rates with adjunctive risperidone LAI during a mean two-year follow-up (175).

Aripiprazole. Aripiprazole monotherapy has demonstrated efficacy for the prevention of manic episodes in the maintenance treatment of patients with BD I and was included in the 2009 guideline as a first-line maintenance therapy for the treatment and prevention of mania (level 1) (3).

A 52-week, relapse prevention RCT demonstrated the efficacy of aripiprazole as an adjunct to lithium or divalproex in patients with manic/mixed episodes and an inadequate response to lithium or divalproex (176). Patients ($n = 337$) in remission for 12 weeks who were randomized to continue adjunctive aripiprazole had a lower rate of relapse to manic (5% versus 15%, $p = 0.013$) but not depressive (10% versus 13%, $p = 0.384$) episodes. Since adjunctive aripiprazole demonstrated efficacy for the prevention of any mood episode or manic episodes, but not depressive episodes, it has been

added as a first-line maintenance therapy for the prevention of manic episodes (level 2).

Another 52-week relapse prevention study in 351 BD I patients with a manic/mixed episode, available in abstract form, showed a non-significant trend to lower rates of manic/mixed relapse with aripiprazole versus placebo added to lamotrigine (11% versus 23%, $p = 0.058$) (177). There was a non-significant trend to lower rates of any relapse, and no effect on depressive relapse rates.

Ziprasidone. An RCT demonstrating the efficacy of adjunctive ziprasidone for maintenance treatment of BD, previously available in abstract form, has now been published (level 2) (178). Adjunctive ziprasidone (80–160 mg/day) demonstrated efficacy for the prevention of manic, but not depressive, episodes.

Second-line options:

Carbamazepine. A meta-analysis of four RCTs, including 464 patients, supports previous conclusions that maintenance treatment with carbamazepine has a similar efficacy to lithium for rates of relapses, with the caveat that there were fewer withdrawals due to adverse effects with lithium (level 2) (179). Given the significant tolerability issues with carbamazepine and the difficulty in combining this agent with other psychotropic medications because of its hepatic microsomal enzyme induction properties, carbamazepine continues to be recommended as a second-line option.

OFC. A six-month, continuation, RCT comparing OFC and lamotrigine monotherapy in patients with bipolar depression that was previously cited in abstract form has now been published (94). OFC was associated with a significantly greater improvement in depressive and manic symptoms, but there were no differences in relapse rates of bipolar depression among responders to acute treatment. In the observational EMBLEM study in 1076 patients with BD mania, adjunctive olanzapine was less effective than olanzapine monotherapy in preventing any relapse (169). By contrast, another study of open-label continuation treatment, in 114 patients with bipolar depression who were responders to OFC found that significantly more patients maintained their response to OFC compared to olanzapine monotherapy (180).

Paliperidone ER. In a three-month continuation study, continued paliperidone ER was significantly more effective than placebo in preventing relapse in prior paliperidone ER responders (level 2) (168).

However, paliperidone ER was less effective in preventing relapse compared to the olanzapine active control group.

Third-line options:

Asenapine. Nine-week and 40-week extension phase results from two pooled three-week RCTs demonstrated the maintenance of benefits with asenapine monotherapy and olanzapine in patients with BD mania (YMRS reduction -24.4 and -23.9 at week 12, -28.6 and -28.2 at week 52, respectively) (level 2) (58, 59). At one year, a worsening of mania was reported in 2.6% of asenapine patients and 1.9% of olanzapine patients, while a switch to a depressive episode occurred in 0% of asenapine and 3.0% of olanzapine patients (59). Time to response was significantly longer with asenapine compared to olanzapine ($p = 0.0127$). In this trial, patients in the placebo groups of the original RCTs were blindly switched to asenapine.

In addition, 40-week extension phase results have now been reported in abstract form from the trial of adjunctive asenapine added to lithium/divalproex compared to placebo (62). Of the original 318 patients, 71 completed the 40-week extension; improvements in mania (-17.2 versus -19.7) and depression (-3.3 versus -3.9) scores at 52 weeks were seen in both the asenapine and placebo groups, but the extension was not powered for statistical comparisons.

Based on evidence of maintenance of benefits, but in the absence of relapse prevention data and clinical experience, asenapine is recommended as a third-line option for maintenance therapy.

Rapid cycling

In a six-month RCT, patients with BD (recent manic episode), SUD, and rapid cycling, who were responders to lithium plus divalproex, were randomized to continue combination therapy or lithium alone (181). Of 149 patients enrolled into the open-label acute stabilization phase, 31 were assigned to maintenance treatment and 55% relapsed. There were no significant differences between combination and monotherapy in the rate of relapse or time to relapse. However, given the small sample size, the study was likely underpowered to detect this.

In the STEP-BD study, among patients who were responders to adjunctive antidepressants and continued this treatment, those with a rapid-cycling course had three times more depressive episodes compared to those without rapid cycling (1.29 versus 0.42 episodes/year, $p = 0.04$) (182).

Mixed states

Several open-label and post-hoc analyses provide additional insight into the role of atypical antipsychotic agents in the management of patients with mixed episodes or psychotic symptoms. In a post-hoc analysis of patients with mixed episodes ($n = 121$), where responders to olanzapine were randomized to continue olanzapine or switch to placebo, there were significant reductions in relapse rates with olanzapine compared to placebo (59.2% versus 91.1%, $p < 0.001$) (183). During 52 weeks of flexible-dosed ziprasidone (40–160 mg/day) open-label extension treatment ($n = 65$), patients with manic or mixed episodes, with or without psychotic symptoms, showed comparable improvements in mania and overall subtypes across subgroups (184). In a 24-week, open-label trial of adjunctive risperidone in 114 patients with mixed or manic episodes, significant reductions from baseline in manic, depressive, and overall symptom scores were observed with combination therapy in both the manic and mixed groups (185).

Section 6. Special populations

Issues in the management of BD in women

The management of BD in women can present additional challenges associated with the reproductive cycle.

Premenstrual syndrome (PMS)/premenstrual dysphoric disorder (PMDD): In the longitudinal STEP-BD study, among women with BD ($n = 293$), those with premenstrual exacerbation had more episodes (primarily depressive), more depressive and manic symptoms overall, a shorter time to relapse, and greater symptom severity (186). Premenstrual exacerbation may predict a more symptomatic and relapse-prone phenotype in women with BD.

A study in 61 women with BD I or BD II and 122 healthy women found that moderate-to-severe PMS/PMDD occurred significantly more frequently in patients with BD II (51.6%) compared to the healthy women (19.7%) (187). Similarly, in a study of 92 women with BD I or BD II, patients with PMDD were more likely to have BD II and cyclothymia than were patients without PMDD (188).

Among patients seen at a specialty gynecology clinic for chronic pelvic pain, those with endometriosis ($n = 27$) were more likely to have BD (44.4%) and a poorer quality of life than women with non-endometriosis pelvic pain ($n = 12$) (0%) (189).

Pre-conception: Providing appropriate education and guidance to patients considering pregnancy or who may have recently become pregnant is an important component of BD management. Pre-conception counseling should include a careful review of risks and benefits and a treatment plan for ongoing monitoring. An analysis of a large claims database including 16385 women of child-bearing age with BD or MDD revealed 1308 women who were receiving a category D (12%) or category X (1%) medication during pregnancy (190). The most frequently used psychotropic drugs were paroxetine, alprazolam, lorazepam, divalproex, lithium, and temazepam.

Pregnancy: The management of pregnant women with BD should incorporate careful planning. Updated recommendations on the use of psychiatric medications during pregnancy and lactation are available from the American Congress of Obstetricians and Gynecologists (ACOG), and the reader is referred to this Practice Bulletin for more information (191). In addition, please visit the Canadian Hospital for Sick Children Motherisk website (<http://www.Motherisk.org>). Therefore, in the following section, we will provide only a brief update of some of the new data in patients with BD.

The risk of teratogenicity associated with use of psychotropic medications (please see ACOG recommendations in Table 6.2) during the first trimester should be carefully weighed against the risks to the mother and the fetus of an untreated mood episode. Psychotropic medications can be used in the second and third trimester if necessary. If lithium is used during the second and third trimester, the serum lithium levels should be monitored closely because of changes in blood volume during pregnancy, and the dose should be adjusted accordingly to maintain levels in the therapeutic range.

Cohort studies in various patient populations confirm the teratogenic risk associated with divalproex (192–194) and carbamazepine (195) during pregnancy. In a case-controlled series of 52 pregnancies, topiramate was associated with reduced birth weight but no decrease in gestational age and no increase in structural defects (196).

Several cohort studies in various patient populations found that, during pregnancy, antidepressants did not confer an increased risk of major congenital anomalies compared to unexposed controls (197, 198). However, in one analysis antidepressant use was associated with increased rates of pregnancy complications, including induced delivery, caesarean section, and preterm

birth, as well as increased risk of persistent pulmonary hypertension of the newborn (199).

Some analyses suggest increased risks with individual antidepressants (198–200), while others do not (197). In one analysis, there were associations of fluoxetine with ventricular septal defects, paroxetine with right ventricular outflow tract defects, and citalopram with neural tube defects, although the absolute risk for these specific effects was small (198). The rate of major anomalies (primarily cardiovascular) in birth outcome among pregnant patients ($n = 314$) with first trimester exposure was 4.7% with fluoxetine and 5.2% with paroxetine, compared to 2.5% in control patients ($n = 1467$), in a multicentre, prospective, controlled study (200). Cardiovascular defects have also been associated with paroxetine (199, 201) and tricyclic antidepressant exposure (199).

A Canadian neonatal record analysis ($n = 119547$ live births) concluded that prenatal exposure to combination therapy with SSRI and benzodiazepines conferred a higher incidence of congenital heart disease when compared to no exposure (202). SSRI monotherapy was not associated with an increased risk for major congenital anomalies, but was associated with an increased incidence of atrial septal defects.

A retrospective chart review including 30092 total deliveries identified one major malformation among 16 of the mothers who were treated with atypical antipsychotic agents during their pregnancy (203). The Food and Drug Administration (FDA) issued a safety alert regarding the risks to newborns associated with prenatal exposure to typical or atypical antipsychotic drugs (204). The new drug labels now contain information about the potential risk for abnormal muscle movements and withdrawal symptoms including agitation, abnormal muscle tone, tremor, sleepiness, breathing, and feeding difficulties in newborns.

In an observational, prospective study in 14 women with BD undergoing maintenance treatment with lithium during pregnancy, the lithium concentration ratio from infant to mother was 0.96 and congenital malformations were greater in those receiving higher doses versus lower doses; however, no significant differences in neonatal outcomes (gestational age/weight, Apgar scores, or hospital stay) were noted (205).

Postpartum period: Distinguishing bipolar depression from MDD can be challenging in the postpartum period because of a lack of screening instruments designed specifically for use during this period (206). A Mood Disorder Questionnaire (MDQ) validation study concluded that, with

Table 6.2. Psychiatric medications in pregnancy and lactation

Agent	Pregnancy risk category ^a	American Academy of Pediatrics rating	Lactation risk category ^b
Anxiolytic medications			
<i>Benzodiazepines</i>			
Alprazolam	D	Unknown, of concern	L3
Chlordiazepoxide	D	N/A	L3
Clonazepam	D	N/A	L3
Clorazepate	D	N/A	L3
Diazepam	D	Unknown, of concern	L3, L4 if used chronically
Lorazepam	D	Unknown, of concern	L3
Oxazepam	D	N/A	L3
<i>Benzodiazepines for insomnia</i>			
Estazolam	X	N/A	L3
Flurazepam	X	N/A	L3
Quazepam	X	Unknown, of concern	L2
Temazepam	X	Unknown, of concern	L3
Triazolam	X	N/A	L3
<i>Non-benzodiazepine anxiolytics and hypnotics</i>			
Buspirone	B	N/A	L3
Chloral hydrate	C	Compatible	L3
Eszopiclone	C	N/A	N/A
Zaleplon	C	Unknown, of concern	L2
Zolpidem	B	N/A	L3
Antiepileptic and mood-stabilizing medications			
Lithium carbonate	D	Contraindicated	L4
Valproic acid	D	Compatible	L2
Carbamazepine	D	Compatible	L2
Lamotrigine	C	Unknown	L3
Antidepressants			
<i>Tricyclic and heterocyclic antidepressants</i>			
Amitriptyline	C	Unknown, of concern	L2
Amoxapine	C	Unknown, of concern	L2
Clomipramine	C	Unknown, of concern	L2
Desipramine	C	Unknown, of concern	L2
Doxepin	C	Unknown, of concern	L5
Imipramine	C	Unknown, of concern	L2
Maprotiline	B	N/A	L3
Nortriptyline	C	Unknown, of concern	L2
Protriptyline	C	N/A	N/A
<i>Selective serotonin reuptake inhibitors</i>			
Citalopram	C	N/A	L3
Escitalopram	C	N/A	L3 in older infants
Fluoxetine	C	Unknown, of concern	L2 in older infants, L3 if used in neonatal period
Fluvoxamine	C	Unknown, of concern	L2
Paroxetine	D	Unknown, of concern	L2
Sertraline	C	Unknown, of concern	L2
<i>Other antidepressants</i>			
Bupropion	B	Unknown, of concern	L3
Duloxetine	C	N/A	N/A
Mirtazapine	C	N/A	L3
Nefazodone	C	N/A	L4
Trazodone	C	Unknown, of concern	L2
Venlafaxine	C	N/A	L3
Antipsychotic medications			
<i>Typical antipsychotic agents</i>			
Chlorpromazine	C	Unknown, of concern	L3
Fluphenazine	C	N/A	L3
Haloperidol	C	Unknown, of concern	L2
Loxapine	C	N/A	L4
Perphenazine	C	Unknown, of concern	N/A
Pimozide	C	N/A	L4

Table 6.2. (Continued).

Agent	Pregnancy risk category ^a	American Academy of Pediatrics rating	Lactation risk category ^b
Thioridazine	C	N/A	L4
Thiothixene	C	N/A	L4
Trifluoperazine	C	Unknown, of concern	N/A
<i>Atypical antipsychotic agents</i>			
Aripiprazole	C	N/A	L3
Clozapine	B	Unknown, of concern	L3
Olanzapine	C	N/A	L2
Quetiapine	C	Unknown, of concern	L4
Risperidone	C	N/A	L3
Ziprasidone	C	Unknown, of concern	L4

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^aThe US Food and Drug Administration classifies drug safety using the following categories: A = controlled studies show no risk; B = no evidence of risk in humans; C = risk cannot be ruled out; D = positive evidence of risk; X = contraindicated in pregnancy.

^bLactation risk categories are listed as follows: L1 = safest; L2 = safer; L3 = moderately safe; L4 = possibly hazardous; L5 = contraindicated.

alternate scoring, the MDQ may be a useful screening instrument for BD in the postpartum period (206, 207). The optimal cut-off score was eight or more endorsed symptoms without the supplementary questions (sensitivity 88% and specificity 85%) (208).

In a well-designed longitudinal study involving 344 pregnant women, there was an 8.4-fold increase in hypomanic symptoms in the early postpartum period (11.7%) compared to during the first trimester (1.4%) and to eight weeks postpartum (4.9%) (209). Although hypomanic symptoms are common in the early puerperium, they are often overlooked, leading to a misdiagnosis of MDD (210). This may be due in part to the absence of hypomania from the postpartum-onset specifier in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition–text revised (DSM-IV-TR) (211). However, a study from Spain suggested reconsideration of the DSM postpartum-onset specifier, as it did not appear to influence prognosis or functioning in women with BD (212).

According to a Danish population-based study of new mothers, the period of highest risk for psychiatric readmission was 10 to 19 days postpartum [relative risk (RR) = 2.7], and the period of lowest risk was during pregnancy (RR = 0.5). Previous diagnosis of BD was the strongest predictor of readmissions 10–19 days postpartum (RR = 37.2), with 27% of women with BD being readmitted within the first year (213). Similarly, psychotic illness has been shown to peak immediately following a first childbirth (214).

ACOG recommendations for the use of psychiatric medications during lactation are also shown in Table 6.2 (191).

Menopause: In a STEP-BD analysis of 164 patients with BD followed for an average of 30 months, menopausal transition was associated with significantly more visits due to depressive symptoms and fewer euthymic visits compared to a comparison group of non-menopausal women and men (215).

Issues in the management of BD in children and adolescents

Complete treatment recommendations for pediatric BD are beyond the scope of these guidelines; the reader is referred to specific guidelines for the management of children and adolescents with BD, such as those developed by the American Academy of Child and Adolescent Psychiatry (AACAP) (216). Therefore, in the following section, we will provide only a brief overview of some of the issues in this population without offering recommendations for levels of treatment.

Presentation and diagnosis: Across the world, BD is the fourth leading cause of disability among adolescents (15–19 years) (217). The presentation and diagnosis of BD in children and adolescents remains controversial. Increasing billing and discharge diagnoses of pediatric BD contradict a stable epidemiologic prevalence, suggesting that diagnostic criteria for BD may not be systematically applied in some clinical settings (218, 219). However, much of the controversy regarding pediatric BD has focused on the group of youth with severe, chronic, non-episode irritability, which has led to the proposed DSM-5 diagnosis of ‘disruptive mood dysregulation disorder’ (DMDD) (220). The reader is referred to recent publications focusing specifically on differential diagnosis and developmental considerations in ascertaining

manic symptoms (221, 222), and regarding concerns about the DMDD diagnosis (223). Prospective studies of children and adolescents with rigorously defined BD demonstrate that this is an episodic illness that continues into young adulthood and is characterized by substantial impairment and morbidity (224–226).

Based on a meta-analysis of 12 epidemiological studies in patients between the ages of seven and 21 years ($n = 16222$), the overall prevalence of BD was 1.8% (219). Of note, rates of BD in these epidemiologic studies did not increase over time and did not differ for studies within versus outside of the USA. Among Canadian adolescents and young adults (15–24 years), the CCHS 1.2 survey recorded a lifetime prevalence of BD of 3.0% (2.1% in those aged 15–18 years; 3.8% in those aged 19–24 years) (227). In a claims database, the one-year rate of a new diagnosis of BD among patients ≤ 17 years of age was 0.23%. Misdiagnosis was common, with 47% being diagnosed with depressive disorder and 37% with disruptive behavior disorder in the previous year (228). In the Course and Outcome of Bipolar Youth (COBY) study ($n = 364$), first episodes in patients ≥ 12 years were generally depressive, while those in patients < 12 years were more likely to be subsyndromal manic/hypomanic symptoms (229).

A claims analysis of younger (age 6–18 years) patients with BD ($n = 423$) showed that the majority did not receive guideline-concordant care, with only 26% receiving anti-manic treatments and 33% receiving antidepressant monotherapy (230). Similarly, eight-year follow-up data from an NIMH study on the course of BD I in children found that 37% of patients had never received anti-manic treatment (231).

Over a five-year follow-up period in the COBY study ($n = 413$) in youth (age 7–17 years), the rate of suicide attempts was 18%. (232). Predictive variables included female gender, severity of depressive symptoms, familial history of depression, and lifetime history of exposure to antidepressants. Non-suicidal self-injury has also been reported in more than 20% of children and adolescents with BD (233).

Comorbidities and mimics: In the COBY study, 44% of youth had at least one lifetime anxiety disorder, and nearly 20% had two or more, with the most prevalent being separation anxiety (24%) and generalized anxiety disorder (GAD) (16%) (234). A family history study that included 157 patients (age 6–17 years) with BD I revealed extremely high rates of comorbid attention-deficit hyperactivity disorder (ADHD) (85%), oppositional

defiant disorder (90%), two or more anxiety disorders (64%), conduct disorder (51%), and SUD (12%) (235).

Early BD onset (age < 12 years) has been associated with ADHD, whereas later BD onset (age ≥ 12 years) was associated with panic, conduct, and SUD (229). Psychotic symptoms have been reported in about one-third of youth with BD, and confer a significantly greater likelihood of lifetime GAD, agoraphobia, social phobia, and obsessive compulsive disorder (OCD) (236).

Medical comorbidities including obesity, type 2 diabetes mellitus, other endocrine disorders, migraine headaches, central nervous system disorders/epilepsy, organic brain disorders/mental retardation, cardiovascular disorders, and asthma in a large cohort study were significantly more prevalent among children and adolescents with BD ($n = 1841$) compared to a control group ($n = 4500$) (237). In the COBY study ($n = 348$), overweight/obesity was seen in 42% of youth with BD, and was associated with increased psychiatric burden (238). Moreover, in a pilot study on inflammatory markers among 30 adolescents in the COBY study, 40% had levels of high-sensitivity C-reactive protein that are considered to confer a high risk for cardiovascular disease among adults ($\geq 2 \mu\text{g/mL}$) (239).

Acute and maintenance treatment of pediatric BD:

Most RCTs in youth with BD have investigated the acute treatment of manic/mixed symptoms, with few assessing maintenance therapy. Thus, taking into account that not all treatments that are efficacious in adults will also be so in children and adolescents, and until further studies become available, the guidelines developed for adults with BD should be cautiously applied to youth.

Psychosocial interventions

The two-year follow-up results of an RCT in adolescent patients ($n = 58$) with BD which compared adjunctive family-focused treatment (FFT) and enhanced care found no differences in time to recurrence of depression or mania, but patients in the FFT group spent fewer weeks in depressive episodes (240). In a one-year open trial, a modified FFT was associated with improved depression, hypomania, and psychosocial functioning scores in youth who were thought to be at high risk for developing BD (241). Preliminary findings suggest that child and family-focused CBT (242), dialectical behavior therapy (DBT) (243), and IPSRT (244) may be promising in the management of BD in this patient population.

Pharmacological management

Atypical antipsychotics. The AACAP published a practice parameter on the use of psychotropic medication in children and adolescents, and the reader is referred to those guidelines for more details (245). Provided below is an overview of current data of the efficacy of atypical antipsychotic agents for the treatment of BD in younger patients.

The US FDA has now approved quetiapine for the first-line treatment of acute manic/mixed episodes in pediatric patients. In light of safety/tolerability concerns, olanzapine (weight gain and metabolic disturbances) and ziprasidone (QT prolongation) were approved as second-line treatments only (246).

A meta-analysis of nine RCTs included 1609 pediatric patients with acute BD mania and found significantly greater improvements in YMRS scores in the atypical antipsychotic agent group and *mood stabilizer* group relative to placebo. The effect sizes were greater for the atypical antipsychotic agent group compared to a *mood stabilizer* group (effect size 0.65 versus 0.20). However, the *mood stabilizer* group included studies on topiramate and oxcarbazepine, neither of which demonstrated efficacy as *mood stabilizers*. Further, medication-associated weight gain was greater with atypical antipsychotic agents than with *mood stabilizers* (effect size 0.53 versus 0.10) (44).

In a small eight-week RCT in 32 adolescents (age 12–18 years), quetiapine monotherapy was not significantly better than placebo for the treatment of bipolar depression (247). This negative trial requires replication in light of the small sample size, high placebo response rates, and robust evidence of quetiapine efficacy in bipolar depression in adults group (1–3). Quetiapine monotherapy has also demonstrated efficacy as acute and maintenance treatment in small, open-label studies (248, 249).

A pooled analysis of four olanzapine trials (two RCTs, two open-label) in adolescents (age 13–17 years) with BD or schizophrenia revealed significantly more weight gain compared to adult patients (7.4 kg versus 3.2 kg) in up to 32 weeks of treatment (250). Adolescents also experienced significant changes in fasting glucose, total cholesterol, triglycerides, alanine aminotransferase, and prolactin. In an eight-week, open-label study the addition of topiramate to olanzapine therapy in 40 pediatric patients with BD resulted in significantly less weight gain than with olanzapine monotherapy, with no differences in mania symptom scores (251).

In addition to the previously cited RCT data, further open-label data support the efficacy and tolerability of ziprasidone therapy in youth with BD (252, 253).

A three-week RCT in 169 pediatric patients with BD mania/mixed episodes demonstrated greater reductions in mania scores with risperidone versus placebo (254). In a six-week RCT in 66 youth, risperidone resulted in more rapid improvement in manic symptoms and a significantly greater rate of remission (63% versus 33%) compared to divalproex (255). Primary outcomes from the eight-week Treatment of Early-Age Mania (TEAM) study of 279 medication-naïve youth (age 6–15 years) with BD I mania/mixed episodes were recently published (256). TEAM was a controlled, randomized, no-patient-choice study comparing lithium, divalproex, and risperidone. The response rate for risperidone (68.5%) was significantly greater than for lithium (35.6%) and divalproex (24.0%), which did not differ significantly from each other. However, increased weight gain, body mass index (BMI), and serum prolactin levels were also significantly greater with risperidone than with the other medications. Similar results were seen in a small cohort study in which risperidone resulted in a faster and greater reduction of symptom scores versus divalproex (257). Hence, although it is premature to conclude that atypical antipsychotic agents have greater efficacy than *mood stabilizers* in pediatric mania, a convergence of data suggest that this may be the case.

An RCT demonstrating the efficacy of aripiprazole for BD I manic/mixed episodes in pediatric patients that was previously cited in abstract form has now been published (258). Another six-week RCT in 43 pediatric patients with BD manic/mixed episodes and comorbid ADHD demonstrated significant reductions in manic, but not depressive or ADHD, symptoms with aripiprazole versus placebo (level 1) (259).

Analyses suggest a poorer response to atypical antipsychotic agent therapy in pediatric patients with BD and comorbid OCD, but not in those with comorbid autism (260, 261).

Anticonvulsants. Several small, open-label trials demonstrated significant improvements with lamotrigine monotherapy in both manic and depressive clinical endpoints (262, 263), and as an adjunct to atypical antipsychotic agents (264) in youth with BD mania/mixed episodes during 3–6 months of follow-up.

A four-week RCT of divalproex ER in 150 pediatric patients (age 10–17 years) with BD mania/mixed episodes found no benefit of active

treatment over placebo on primary or secondary outcomes, and there was only modest improvement in mania scores during the six-month, open-label extension phase (265). However, a six-month, open-label study in 226 youth with BD I mania/mixed episodes found that divalproex ER reduced mania scores and was generally well tolerated (266).

In an eight-week, open-label trial in 27 youth with bipolar spectrum disorders, carbamazepine ER was associated with improvements in mania, depression, psychosis, and ADHD symptoms, but drop-out rates were high (267).

Issues in the management of BD in older patients

Presentation and course: The two-year EMBLEM study included 475 patients > 60 years with acute BD mania/mixed, and found that older patients had a history of more rapid cycling, fewer suicide attempts, and less severe manic and psychotic symptoms, but no difference in depressive symptomatology (268). Older patients with late-onset BD (age ≥ 50 years) experienced a better 12-week outcome with a faster recovery and earlier discharge compared to older patients with early-onset BD (age < 50 years). The prevalence of mixed episodes was reported at 10% in patients ≥ 60 years in an RCT (269).

Comorbidity: In a case-controlled study, there was a higher prevalence among older patients (n = 82, age > 60 years) with BD of diabetes mellitus (27%), atopic diseases (20%), smoking (24%), and unfavourable social functioning (22%) when compared to age-matched controls (270).

A large survey of geriatric patients in a Veterans Health Administration database found the use of anticonvulsants to be associated with an over twofold increased risk of fracture. In addition, patients with BD had a 20% increased risk of fracture compared to those without BD, independent of the use of anticonvulsants (271).

Older adults with BD have been shown to have greater levels of cognitive dysfunction than age-matched mentally healthy control subjects (272–275). Among older patients with BD, a greater burden from vascular risk factors has been associated with poorer outcomes on some cognitive measures (276, 277). Several analyses have failed to detect a significant association between dementia or cognitive performance in older patients and the use of lithium (277, 278).

Treatment of BD in older patients: Data assessing pharmacotherapy specifically in older patients with BD remain scarce. In a post-hoc, pooled

analysis of two quetiapine monotherapy RCTs in patients with acute BD mania, subgroup analysis of 59 older adults (age ≥ 55 years) demonstrated a significant improvement in manic symptoms as early as day four, and this was sustained over the 12 weeks of follow-up versus placebo (279).

At 12 weeks, the results from an open-label study of adjunctive lamotrigine in older patients (n = 57, age ≥ 60 years) with BD I or BD II indicated an overall significant decline in depressive symptoms, with a 65% response rate and a low rate of discontinuations because of adverse events (10%) (280).

Issues in the management of BD in patients with comorbid conditions

The reader is also referred to a task force report on the management of patients with mood disorders and comorbid psychiatric and medical conditions developed by the CANMAT Comorbidity Task Force (281).

Prevalence and impact

Medical. In the large US National Epidemiologic Survey on Alcohol and Related Conditions study, which included 1548 patients with BD I, the prevalence of one or more general medical conditions was 32% (282). In another analysis, patients with BD I or BD II were found to have a mean of 2.5 comorbid medical conditions (283). Cardiovascular disease and hypertension were almost fivefold more prevalent among patients with BD than controls (284). The risk of cardiovascular mortality was found to be more than double in patients with BD I compared to those with BD II, in a long-term follow-up study (285). In addition, patients with BD had a significantly greater risk for hospital readmission due to a cardiovascular event (286).

The increased rate of metabolic syndrome in patients with BD, by up to twofold compared to the general population, has been documented in countries around the world (287). Comorbid metabolic disturbances in patients with BD have been associated with a more complex illness presentation, less favourable response to treatment, and worse course of illness (283, 287, 288).

In patients with BD, a higher BMI has been associated with more frequent manic and depressive relapses, more suicide attempts, and poorer psychosocial functioning, as well as a greater frequency of type II diabetes, hypertension, and subthreshold anxiety disorders (289–291). Over-

weight/obesity has also been shown to have a negative impact on long-term treatment response (283, 289) and on cognitive function in euthymic patients with BD (292).

Comorbid migraine affects nearly one in four patients with BD (293), and confers significantly increased risk for suicidal behavior, comorbid psychiatric disorders, and rapid cycling, as well as a greater number of mood episodes and lifetime hospitalizations compared to patients without migraine (293, 294). The prevalence of migraine is reportedly higher in patients with BD II than in those with BD I (35% versus 19%) (293).

Up to 12% of patients with epilepsy may have a diagnosis of BD; however, only 1.4% had *pure* BD, as all other cases were associated with differing states relating to the primary diagnoses of epilepsy (295).

Psychiatric. A retrospective analysis of four trials including 566 patients with rapid-cycling BD I or BD II found lifetime rates of anxiety disorders and SUD of 46% and 67%, respectively (296). Comorbid SUD has been linked to an increased risk of suicide and other unnatural deaths, suicide attempts, nicotine dependence, and other SUDs in patients with BD (297–299). Patients with BD have a fivefold higher risk of current cigarette smoking compared to the general population (300). Cigarette smoking has also been associated with suicidal behavior in patients with BD (301, 302). In addition, suicidal behavior has been associated with borderline personality disorder (BPD), panic disorder, alcoholism, other drug addictions, and GAD, although only BPD and alcoholism were independently associated (301). Comorbid SUD in patients with BD confers substantially greater impairment in social functioning compared to patients without SUD (303).

In patients with rapid-cycling BD, comorbid SUD was associated with a twofold increased risk of being incorrectly medicated (not receiving a *mood stabilizer* after the onset of first mania/hypomania) (296). In addition, an uncontrolled study suggested that comorbid SUD may be associated with a very high risk of antidepressant-induced switch to mania (76%) (304, 305).

A functional assessment of patients ($n = 206$) with BD I or BD II noted that more than one-third had missed ≥ 2 years of work time over a five-year period, and extended unemployment was associated with increased rates of panic disorder and alcohol abuse (306). The presence of comorbid panic disorder in patients with BD I (compared to those with no panic disorder) was associated with significantly more depressive, manic, and any mood episodes, as well as increased risk of lifetime SUD or eating

disorders (307). In the NIMH Collaborative Depression Study, the presence of psychic and somatic anxiety symptoms was associated with a greater proportion of weeks in depressive episodes during long-term follow-up (mean 17 years) of patients with BD (308). The prevalence of lifetime eating disorders, particularly binge eating disorder, is high (14%) in patients with BD (309).

It is of note that patients with BPD are at high risk of being misdiagnosed as having BD, and vice versa (310, 311).

The International Mood Disorders Collaborative Project reported the prevalence of lifetime ADHD in adults with BD as 18%, which was substantially higher than that found in patients with MDD (5%). Comorbid ADHD has been associated with a greater number of comorbid psychiatric conditions (312), a negative impact on the course of BD in adulthood (313), impaired psychosocial functioning, and poorer overall quality of life (312, 314).

Treatment of BD in patients with comorbidities: In a retrospective analysis, a bipolar collaborative chronic care model was as effective in patients with BD and comorbid conditions (SUD, psychiatric, and/or medical) as in those without, although it may be necessary to pay specific attention to physical quality of life in patients with cardiovascular disease (315). A six-month pilot study of a BD medical care model demonstrated a slowing of decline in physical health-related quality of life compared with usual care in patients with BD and cardiovascular disease-related risk factors (316). Improvements in mental health-related quality of life were also seen, but were not significant.

Medical. A small ($n = 10$), 14-week pilot study of an integrated psychosocial treatment model including three treatment modules (nutrition/weight loss, exercise, and wellness treatment) administered in group sessions, as well as weekly exercise, demonstrated improvements in quality of life, depressive symptoms, and weight (317). Open-label adjunctive ziprasidone was effective in significantly improving weight-related parameters while maintaining or improving mood symptoms in 25 obese/overweight patients with BD taking atypical antipsychotic agents, lithium, or divalproex (318).

In a recent report, bariatric surgery for weight reduction was as effective in patients with BD as in those without (319).

Psychiatric. An RCT in 61 patients with BD and comorbid SUD compared a modified version of

integrated group therapy (12 sessions instead of 20) to group drug counseling (320). The integrated group therapy, which employed a cognitive-behavioral model integrating treatment of both conditions, resulted in an increased likelihood of achieving total abstinence and a better overall composite outcome compared to regular group counseling. A review of psychosocial interventions for the treatment of comorbid anxiety in patients with BD concluded that CBT, mindfulness-based CBT, and relaxation training may be effective, while interpersonal and family therapy, and psychoeducation alone did not seem to be beneficial in treating comorbid anxiety (321).

Two large, 12-week RCTs ($n = 362$ and $n = 115$) of adjunctive quetiapine in patients with BD and comorbid alcohol abuse or dependence did not show significant improvements in measures of alcohol use and dependence compared to placebo, although depressive symptoms improved in one trial (322, 323). A 12-week RCT of adjunctive naltrexone in 50 patients with BD I or BD II and comorbid alcohol dependence demonstrated a trend toward greater decrease in alcohol-related outcomes compared to placebo (324). Response to naltrexone was significantly related to medication adherence.

In a 20-week RCT involving 80 patients with BD and comorbid SUD (cocaine or methamphetamine dependence), both quetiapine and risperidone improved manic and depressive symptoms, as well as drug cravings and use, with no significant differences between treatments (325); however, this study lacked a placebo group. In another placebo-controlled, 12-week RCT, involving 44 patients with BD I or BD II and cocaine dependence, citicoline significantly improved some aspects of declarative memory and cocaine use, but not mood (326).

In a small RCT involving 31 patients with rapid-cycling BD and comorbid SUD who were stabilized on the combination of lithium plus divalproex, there was no significant difference in mood relapse rates between patients randomized to continue combination therapy and those who received lithium alone (181). An analysis of 98 patients from the acute open-label phase of this study found that these

patients have a poor response to treatment and a high burden of serious medical comorbidity (327).

A small, six-week RCT in 43 pediatric patients with BD manic/mixed episodes and comorbid ADHD demonstrated significant reductions in manic, but not depressive or ADHD, symptoms with aripiprazole versus placebo (level 1) (259).

In a randomized, crossover trial in 16 youth with BD (age 8–17 years) who had responded to aripiprazole, the addition of methylphenidate did not result in significant improvements in ADHD or mania symptoms compared to placebo (328); however, depressive symptoms did improve.

In an eight-week RCT of risperidone in 111 patients with BD and comorbid panic disorder or GAD, risperidone was no more effective than placebo on any of the anxiety measures (329).

A post-hoc analysis of the BOLDER I and BOLDER II trials including 1051 patients with BD I or BD II depression reported significant improvements in anxiety symptom scores as early as week one, and these were sustained through week eight with quetiapine compared to placebo (330). This suggests that quetiapine should be investigated in patients with BD and comorbid anxiety disorders.

Section 7. Acute and maintenance management of bipolar II disorder

Acute management of hypomania

The preponderance of depressive symptoms in patients with BD II likely contributes to the under-investigation of treatments for hypomania in this patient group. The only studies carried out to date examined mixed samples of patients with BD I and BD II and did not report results separately for BD II. Nonetheless, due to the paucity of information on the treatment of hypomania, we will describe them briefly here. Two small, eight-week RCTs indicated that quetiapine ($n = 39$) (331) and divalproex ER ($n = 60$) (332) were superior to placebo in treating patients with hypomania or mild mania. In addition, a previously described six-month, open-label trial suggested efficacy for risperidone (333).

Table 7.2. Recommendations for pharmacological treatment of acute bipolar II depression

First line	Quetiapine, quetiapine XR^a
Second line	Lithium, lamotrigine, divalproex, lithium or divalproex + antidepressants, lithium + divalproex, atypical antipsychotic agents + antidepressants
Third line	Antidepressant monotherapy (primarily for those with infrequent hypomanias), switch to alternate antidepressant, quetiapine + lamotrigine^a , adjunctive ECT^a , adjunctive NAC^a , adjunctive T3^a
Not recommended	See text on antidepressants for recommendations regarding antidepressant monotherapy

ECT = electroconvulsive therapy; NAC = N-acetylcysteine; T3 = triiodothyronine; XR = extended release.

^aNew or change to recommendation.

Due to the methodological limitations of these trials, and the lack of systematic study of many commonly used mood-stabilizing medications, it is difficult to formulate evidence-based treatment recommendations for hypomania. However, clinical practice suggests that medications that are effective in mania are efficacious in treating hypomanic symptoms. Thus, in patients with persistent and/or impairing symptoms of hypomania, clinicians should treat according to their clinical judgment, using lithium, divalproex, or atypical antipsychotic agents and tapering potentially contributory medications such as antidepressants.

Acute management of bipolar II depression

Psychotherapy: The role of psychotherapy in the treatment of BD II depression has also been understudied. Nonetheless, the predominance of depressive symptoms in patients with BD II, and the fact that BD II depression shares many clinical characteristics with MDD suggest that psychotherapy may improve outcomes in these patients. Supporting this is one small ($n = 17$), 12-week feasibility study demonstrating that 41% of patients with BD II depression achieved a response ($\geq 50\%$ reduction in depression scores) with IPSRT monotherapy without an increase in mania scores (334).

Pharmacotherapy: Table 7.2 illustrates the recommendations for the pharmacological treatment of acute BD II depression (1–3). Quetiapine XR joins quetiapine as a first-line option. Quetiapine plus lamotrigine, adjunctive NAC, and adjunctive triiodothyronine (T3) have been added as third-line options.

First-line options

Quetiapine. The four large RCTs demonstrating the efficacy of quetiapine monotherapy in combined groups of patients with BD I or BD II depression, which were cited in previous iterations of these guidelines, have now all been published: BOLDER I (88) and II (89), and EMBOLDEN I (90) and EMBOLDEN II (91). A pooled analysis of data in 776 patients with BD II from all four studies has been presented in abstract form (level 1) (335). Quetiapine doses of 300 mg/day and 600 mg/day were both associated with significantly greater improvements in MADRS total scores compared to placebo, beginning at week one and continuing through week eight. Response and remission rates were also significantly greater with both doses of quetiapine than placebo. There were

significant improvements in core depressive symptoms, including reported sadness, anhedonia, negative thoughts, and suicidality, as well as anxiety symptoms.

In an eight-week RCT in patients with BD I and BD II depression, among the patients with BD II ($n = 53$), quetiapine XR 300 mg/day was associated with a significantly greater improvement in MADRS total score at study end compared to placebo (level 2) (92).

Second-line options

Lithium. The EMBOLDEN I trial included a lithium comparator arm, and provides the only placebo-controlled, parallel-group RCT data for lithium in acute BD II depression (90). In this trial, neither lithium nor quetiapine were superior to placebo in improving depression scores in patients with BD II, raising the possibility that this was a failed, rather than negative, trial. In addition, the mean lithium levels were < 0.8 mEq/L.

Divalproex. A meta-analysis of four small studies (total $n = 142$) in patients with BD I or BD II depression found that the RR of response was double, and of remission almost two-thirds greater, with divalproex monotherapy compared to placebo (96). Two of the trials reported results separately for BD I and BD II, with one reporting greater improvement in patients with BD I than BD II (as outcomes for the BD II group showed no separation from placebo) (336), and the other reporting greater improvements in BD II than BD I (337). Additional, open-label data supporting the efficacy of divalproex ER in BD II depression, previously cited in abstract form, have now been published (338). Thus, the data in aggregate are mixed. Further studies are clearly warranted to fully understand the role of divalproex in BD II depression.

Lamotrigine. The results of two previously unpublished RCTs of lamotrigine have been published in a review article (339). In the first study, 221 patients with BD II received lamotrigine 200 mg/day or placebo for eight weeks, while in the second 206 patients with BD I or BD II depression were randomized to lamotrigine 100–400 mg/day or placebo. In neither trial was lamotrigine superior to placebo. The negative results may be related to the slow titration of lamotrigine and high placebo response rates. Further, a meta-analysis of lamotrigine trials in BD I or BD II depression showed greater response

rates with lamotrigine than placebo, although the effect size was very modest (83). Based on this evidence, and its excellent tolerability profile, lamotrigine continues to be recommended as a second-line option for the acute treatment of BD II depression.

Third-line options

Antidepressant monotherapy. Relatively few studies have assessed antidepressant monotherapy in BD II because of concerns about induction of mood elevation. A paroxetine comparator arm in the EMBOLDEN II trial represents the largest placebo-controlled sample to evaluate antidepressant monotherapy in BD II depression (91). Paroxetine was not superior to placebo, although the dose may be considered low (20 mg), and quetiapine did not separate from placebo in this study, suggesting that this was a failed, rather than negative, study. Interestingly, switch rates into hypo/mania were similar with paroxetine and placebo.

In a 14-week, open-label study of fluoxetine monotherapy (n = 148), 60% of patients responded and 58% remitted (340). Although about 24% experienced hypomania/subsyndromal hypomania, this did not result in treatment discontinuation. In a post-hoc analysis of a previously reported open-label study in 83 patients with BD II, the significantly greater improvements in depression scores with venlafaxine compared to lithium were independent of rapid-cycling status, and venlafaxine did not result in a higher proportion of mood conversions (versus lithium) in either the rapid or non-rapid-cycling patients (341). Patients in this study who were unresponsive to lithium therapy (n = 14) and who were subsequently crossed over to venlafaxine experienced significantly greater reductions in depression and overall mood scores, with no differences in mania scores versus prior lithium (342). The main limitation of these studies is their open-label design.

Quetiapine + lamotrigine. A 12-week, open-label trial assessed the benefit of adding lamotrigine or quetiapine to pre-existing therapy in a mixed sample of patients with BD (BD I n = 15, BD II n = 22, or BD NOS n = 1) on multiple medications (level 3) (104). Adding quetiapine to lamotrigine in patients who had not responded to lamotrigine (n = 17 patients with BD II), and adding lamotrigine to quetiapine in patients who had not responded to quetiapine, was associated with improvements in the overall sample (level 3) (104). Data were not reported separately for patients with BD II.

Adjunctive ECT. An open-label study of twice-weekly bilateral ECT included patients with BD II who were medication refractory (n = 67). They achieved a response rate of 79% and a remission rate of 57% (343). This response rate was intermediate between patients with MDD (94%) and those with BD I (67%).

Novel treatments. In a sub-analysis of a small number of patients with BD II (n = 14) participating in a 24-week RCT, significantly more patients achieved full remission of both depressive and manic symptoms with adjunctive NAC compared to placebo (344). In a retrospective chart review of patients with treatment-resistant BD II or BD NOS depression (n = 159), treatment with supraphysiologic doses of T3 was associated with response in a majority of patients (345).

Maintenance therapy for bipolar II disorder

Psychotherapy: A post-hoc analysis of 20 patients with BD II who participated in a single-blind RCT demonstrated the benefits of adjunctive psychoeducation (21 sessions over six months) compared to unstructured support groups, with lasting benefits for up to five years (346). Significantly fewer patients in the psychoeducation group experienced any mood, depressive, or hypomanic relapse during follow-up, and had significantly better psychosocial functioning at both two- and five-year follow-up.

Pharmacotherapy: The major focus of maintenance therapy for patients with BD II is prevention of depressive episodes. New data support the addition of quetiapine monotherapy as first-line, and adjunctive quetiapine as second-line options for maintenance treatment for BD II (Table 7.4) (1–3). Lithium and lamotrigine continue to be recommended as first-line agents and fluoxetine has been added as a third-line treatment option.

First-line options

Quetiapine. A pooled analysis of maintenance data from the EMBOLDEN I and II trials has been presented in abstract form (335). Among patients with BD II (n = 231) who achieved remission during acute-phase treatment with quetiapine, those who continued quetiapine monotherapy for up to 52 weeks were significantly less likely to experience relapse into any mood episode [hazard ratio (HR) 0.47 for 300 mg and 0.18 for 600 mg] or depressive mood episode (HR 0.35 and 0.21) compared to those who switched to placebo (level 1).

Table 7.4. Recommendations for maintenance treatment of bipolar II disorder

First line	Lithium, lamotrigine, quetiapine^a
Second line	Divalproex; lithium or divalproex or atypical antipsychotic + antidepressant; adjunctive quetiapine^a ; adjunctive lamotrigine^a ; combination of two of: lithium, divalproex, or atypical antipsychotic
Third line	Carbamazepine, oxcarbazepine, atypical antipsychotic agent, ECT, fluoxetine^a
Not recommended	Gabapentin

ECT = electroconvulsive therapy.

^aNew or change to recommendation.

Rates of mania/hypomania were low, and similar for quetiapine and placebo.

Second-line options

Adjunctive lamotrigine. In a 52-week, open-label study in 109 patients with treatment-refractory BD II, adjunctive lamotrigine was associated with a significant improvement in depressive symptoms and sustained response (level 3) (347). Depressive symptoms continued to improve over a 52-week period, suggesting that the two negative acute-phase RCTs discussed above may have been too short to detect a difference between lamotrigine and placebo. Similarly, a retrospective chart review reported that the majority of 31 patients with treatment-resistant BD II depression who received adjunctive lamotrigine for ≥ 6 months were much or very much improved (348). The mean dose of lamotrigine was 199 mg/day and the maximum 400 mg/day, suggesting that a substantial number of patients required ≥ 200 mg for maximal benefit.

Adjunctive quetiapine. Naturalistic studies in combined populations of patients with BD I and BD II demonstrated high rates of sustained euthymia with adjunctive quetiapine, in spite of the fact that the quetiapine doses used in clinical practice were substantially lower than those used in clinical trials (level 3) (349, 350). Unfortunately, neither of these studies reported separate results for patients with BD II.

Third-line options

Carbamazepine/oxcarbazepine. In an RCT in BD I (n = 27) or BD II (n = 25) patients who displayed residual manic or depressive symptoms on maintenance lithium treatment, the addition of eight weeks of carbamazepine or oxcarbazepine resulted in significant symptom reduction, with oxcarbazepine being more effective than carbamazepine (67). Results were not presented separately for patients with BD II.

Fluoxetine monotherapy. There are now two small RCT extension studies with fluoxetine in patients

with BD II depression. The first was a six-month RCT in patients with BD II and BD NOS who had responded to fluoxetine, in which relapse rates were 43% with continued fluoxetine versus 100% with placebo (p = 0.08) (351). The second was a one-year RCT (n = 81) in patients with BD II depression who had responded to fluoxetine. It reported that patients were significantly more likely to remain well if they continued on fluoxetine than if they switched to lithium (352). However, neither fluoxetine nor lithium was significantly better than placebo in mean time to relapse (fluoxetine 249.9 days, lithium 156.4 days, placebo 186.9 days). The lack of superiority of fluoxetine over placebo in these studies may be related to a lack of statistical power due to a smaller sample size.

Data from STEP-BD and other naturalistic studies provided additional information on the efficacy and safety of antidepressants in real-world settings. In a STEP-BD randomized, open-label trial, patients with depressive symptoms (n = 70; n = 21 with BD II) who responded acutely to adjunctive antidepressants had a significantly longer time until relapse into depression if they continued the antidepressant for 1–3 years versus discontinuing after resolution of the depression (182). Patients with BD II in this trial showed similar benefits to those with BD I, with no increase in hypo/manic switch. Similarly, in the entire STEP-BD sample (n = 3640; 30.7% with BD II), there was no increased frequency of switch from depression to hypo/mania without an intervening period of wellness in antidepressant-treated patients (19.6%) compared to patients receiving non-antidepressant treatments (24.9%) (353). Consistent with previous studies (354), the risk of antidepressant-associated switch was lower in BD II than BD I. The results from another open-label study in patients with BD II who discontinued antidepressant treatment showed that relapse occurred 2.5 times more quickly when discontinuation was rapid versus gradual (355).

ECT. Information on the use of ECT in BD II remains limited. In one small case series of 14 patients with rapid-cycling BD (nine with BD II) who received maintenance ECT for a mean of

21 months, all patients experienced significant improvement and a resolution of rapid-cycling status (356).

Clinical questions and controversies

Is cognitive dysfunction an issue in patients with BD II?

Persisting cognitive dysfunction is common and debilitating in patients with BD II. In a meta-analysis, patients with BD II had lower performance scores than healthy controls in all cognitive domains (357). In addition, cognitive impairment in BD II was as severe as in BD I, with the exception of memory and semantic fluency.

In a case series of 58 BD I, BD II, or BD NOS patients who received donepezil for memory problems, 84% with BD II (36/43) showed improvement, compared to 0% of patients with BD I (0/7) and 50% of patients with BD NOS (4/8) (358). More than half of the patients with BD I had worsening of affective symptoms compared to only 2% of those with BD II and 25% of those with BD NOS.

Do the clinical features of depressive episodes inform treatment decisions in BD II?

Data from STEP-BD show that mixed hypomanic symptoms are common during depressive episodes, occurring in 70% of patients with BD II, compared to 66% of patients with BD I (129). Adjunctive antidepressants did not lead to greater recovery rates among patients with mixed symptoms in STEP-BD, and were in fact associated with greater manic symptom severity at the three-month follow-up (359). Although recovery rates were not reported separately for patients with BD II in this sample, this suggests that antidepressants should be avoided in BD II depressive episodes with concomitant hypomanic symptoms.

Psychotic symptoms are also relatively common in BD II depression, and were present in 20% of patients with BD II in a Spanish study (n = 164) (360). There is little information to guide the treatment of psychotic depression in patients with BD II, but clinical experience and studies in MDD suggest that antipsychotic medications either as monotherapy (e.g., quetiapine) or in combination with mood stabilizers may be required.

Bipolar spectrum disorders

Diagnosis: Formulating treatment recommendations for patients with bipolar spectrum disorders

(BSDs; also referred to as 'BD NOS' in the DSM-IV) remains hampered by both a lack of consensus regarding which disorders should be included in this category, and also an almost complete absence of well-designed clinical trials in this patient group. The issue is further compounded by uncertainty regarding the diagnostic stability of BSDs. In fact, BSDs may be prodromal to BD I and BD II in a substantial number of patients, according to one longitudinal study of 57 people with cyclothymia or BD NOS, where 42% progressed to BD II and 10% to BD I over a 4.5-year follow-up period (361).

Epidemiology: The results from two large studies which measured the prevalence of BSDs indicate that they are relatively common in the general population. The World Mental Health Survey Initiative, including 61392 people in nine countries in North and South America, Europe, and Asia, reported that 1.4% of the population met lifetime criteria for subthreshold BD (4). This was similar to the lifetime prevalence of 2.4% reported in the National Comorbidity Survey Replication (NCS-R) in the USA (n = 9282) (362). In both studies, the prevalence of BSDs was greater than those of BD I and BD II combined. The NCS-R further suggested that BSDs are also common in clinical populations, as over 35% of people with major depressive episodes also met the lifetime criteria for subthreshold hypomania (363). Although a liberal definition of subthreshold hypomania was utilized (lifetime presence of ≥ 1 hypomanic symptom), the NCS-R reported that, compared to people with major depressive episodes alone, those who had subthreshold hypomania shared a number of clinical features with those suffering from BD I or BD II, including an earlier age of onset, more frequent depressive episodes, a greater number of suicide attempts, and higher rates of comorbidity.

Management: Very few studies have investigated treatment options for BSDs. The only RCT that has been reported to date was conducted in 56 youth with BSD or cyclothymia who were randomized to divalproex or placebo for up to five years. At study end there were no differences between treatment groups in time to study discontinuation due to a mood episode or for any reason, severity of mood symptoms, or psychosocial functioning (364).

A small case series reported rapid and sustained symptom remission in four patients with BD NOS and depressive or mixed symptoms with low-dose quetiapine (50–75 mg) (365). In addition, a

retrospective chart review of 34 patients with treatment-refractory BD NOS found that adjunctive treatment with supraphysiologic doses of T3 was associated with an improvement in depressive symptoms in 85% of patients, and remission in 38% (345). In a case series of 58 patients with BD prescribed donepezil for memory problems, 50% of those with BD NOS (4/8) had improvements in memory; however, 25% had a worsening of affective symptoms (358).

In the absence of well-designed clinical trials, specific treatment suggestions for patients with BD NOS cannot be made. Clinicians should formulate treatment plans based on patients' presenting symptoms, course of illness, previous treatment responses, and family history. Given the probability that subthreshold bipolarity is present in a substantial proportion of patients with MDD, clarifying the nature and best treatment options for BD NOS is a major unmet need in mood disorders research.

Section 8. Safety and monitoring

Monitoring

Previous iterations of the guidelines provided recommendations for initial and follow-up laboratory investigations and monitoring strategies for patients with BD (1–3). BD and some of its treatments can increase the risk of comorbid medical conditions, as well as risk factors for cardiovascular disease such as overweight/obesity, diabetes, metabolic syndrome, and dyslipidemia. Complete medical and laboratory investigations should be performed at baseline, with ongoing monitoring for weight changes and adverse effects of medication.

The ISBD has also published consensus recommendations for general safety monitoring for all BD patients receiving treatment, as well as specific monitoring recommendations for individual agents, and the reader is also referred to this document for more details (366).

Unfortunately, the UNITE global survey of 1300 patients with BD found that monitoring of safety parameters does not occur in the majority of patients, with less than 30% undergoing weight and blood pressure measurements, and less than 5% undergoing a physical examination or blood tests during interactions with their principal health care provider (11).

Safety and tolerability of pharmacotherapy for BD

The previous iterations of the guidelines have extensively reviewed the safety and tolerability of

pharmacotherapeutic options; only new data are included here (1–3).

An analysis of 48 RCTs in patients with BD or schizophrenia found that, compared to risperidone, quetiapine was associated with significantly less anxiety, restlessness, and extrapyramidal symptoms (EPS); and also compared to risperidone, olanzapine was associated with increased weight gain and ziprasidone with decreased weight gain (367).

Weight gain: The naturalistic STOP-EM trial concluded that, in 47 patients with BD receiving maintenance therapy following their first manic episode, the mean 12-month weight gain was significantly greater compared to healthy control subjects (4.76 kg versus 1.50 kg; $p = 0.047$). In addition, 12-month rates of overweight/obesity were $> 50\%$ in patients with BD, almost double those in healthy subjects (368).

A review of RCTs confirmed that long-term olanzapine treatment (≥ 48 weeks) was associated with a substantial weight gain (mean 5.6 kg), with 64% of patients gaining $\geq 7\%$ of their baseline weight (369). During short-term treatment, olanzapine orally disintegrating tablet was not associated with any reduction in weight gain compared to the standard tablet formulation (370). By contrast, a post-hoc analysis of a six-month RCT found that adjunctive ziprasidone had no negative impact on metabolic parameters or body weight compared to adjunctive placebo (371). Post-hoc analyses of two studies found a modest increase in weight with adjunctive aripiprazole that was not significantly different from that using lithium/divalproex alone (372). When used as an adjunct to lamotrigine, aripiprazole plus lamotrigine was associated with an increased weight gain compared to lamotrigine alone, which was associated with decreased body weight over the one-year period.

The non-randomized Second-generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth cohort study found that after a median of 10.8 weeks of treatment, weight increased by 8.5 kg with olanzapine ($n = 45$), 6.1 kg with quetiapine ($n = 36$), 5.3 kg with risperidone ($n = 135$), and 4.4 kg with aripiprazole ($n = 41$) compared to 0.2 kg in the untreated group ($n = 15$) (373).

An 11-month, RCT in 50 patients on pharmacotherapy for BD found that a multimodal lifestyle intervention (11 group sessions and weekly fitness training) significantly reduced BMI, at end of treatment (five months) and at a six-month follow-up, compared to a wait-list control group; however, the effect was only significant in women (374).

Metabolic syndrome and type 2 diabetes: Additional data continue to demonstrate high rates of diabetes and metabolic syndrome associated with atypical antipsychotic agent use in patients with BD (375). However, in a post-hoc analysis of a six-month RCT, the incidence of metabolic syndrome with aripiprazole maintenance therapy was similar to that of placebo (376).

Additional data confirm the potential for metabolic disturbances with divalproex treatment. In a cohort study, divalproex was associated with significantly higher plasma insulin, triglyceride levels, and BMI, as well as lower fasting glucose and high-density lipoprotein cholesterol (HDL-C) levels (377).

Dyslipidemia: Dyslipidemia is an important cardiovascular risk factor. As discussed in previous iterations of the guidelines, atypical antipsychotic agents, as well as lithium/divalproex, can cause dyslipidemia (1–3). Additional data from a cohort study found that divalproex was associated with low HDL-C levels and high adiponectin levels in patients with BD compared to non-psychiatric matched control subjects (378). Lipid profiles should be monitored and appropriate lipid-lowering medications prescribed as needed, according to published recommendations for the management of dyslipidemia.

Endocrine side effects: The results from a case-controlled study indicated higher risks of hypothyroidism in patients with BD who had used carbamazepine alone [odds ratio (OR) = 1.68], combination lithium and valproate (OR = 2.40), combination lithium and carbamazepine (OR = 1.52), or all three agents (OR = 2.34) compared to patients who had never used any of these agents (379). A meta-analysis of 390 RCTs and observational studies found that lithium was associated with an increased risk of clinical hypothyroidism (OR = 5.78), as well as increases in thyroid-stimulating hormone and parathyroid hormone (380).

Suicide: A 2.5-year RCT of 98 patients with BD and past suicide attempts found no significant differences between lithium and divalproex in time to suicide attempt or suicide event, although the trial was statistically underpowered to detect differences (381).

Cognitive impairment: Three meta-analyses have demonstrated persistent cognitive impairments in euthymic patients with BD, including deficits in executive functions, verbal memory, learning, processing speed, and attention (357, 382, 383).

In addition, patients tested during a manic/mixed or depressed state showed exaggerated impairment on measures of verbal learning (383).

Several cohort studies have demonstrated greater cognitive dysfunction in euthymic patients with BD taking antipsychotic medications compared to healthy control subjects (384–386) or to those not taking antipsychotic agents (385). Two cohort studies have shown fewer cognitive impairments associated with quetiapine than with olanzapine or risperidone (385, 387).

An eight-week RCT in 35 euthymic patients with BD found that adjunctive pramipexole significantly improved visual-verbal processing speed and working memory compared to placebo (388). A small ($n = 16$), three-month RCT in minimally symptomatic patients with BD found that adjunctive galantamine improved episodic memory performance; however, placebo improved processing speed (389).

Hypersensitivity and dermatological reactions: Additional data demonstrate the risk of serious rash, erythema multiforme, Stevens–Johnson syndrome, or toxic epidermal necrolysis with lamotrigine, carbamazepine, and divalproex (390, 391). A 12-week trial demonstrated a statistically significant reduction in the development of rashes with a slow titration of lamotrigine compared to a standard titration schedule (392).

The US FDA issued a warning that type I hypersensitivity reactions (including anaphylaxis and angioedema) can occur with asenapine use, after as little as one dose (393).

Sedation: In a pooled analysis of data from three short-term trials in patients with BD, asenapine monotherapy and as an adjunct was associated with higher rates of somnolence than placebo, which occurred after 1–9 days of treatment and persisted for 1–4 weeks (394).

Gastrointestinal symptoms: In a three-month RCT, ER carbamazepine resulted in significantly fewer autonomic and gastrointestinal adverse events compared to the immediate-release formulation (64).

Neurological side effects including EPS: An increased risk of neuroleptic malignant syndrome associated with the use of antipsychotic medications (OR = 2.36) has been reported in patients with BD (395).

A post-hoc analyses of pooled data in patients with a mood disorder reported an increased rate of akathisia in patients receiving aripiprazole (18%) compared to placebo (5%) (396).

Fracture risk: In a Veteran's Administration prospective cohort study, the use of anticonvulsants was associated with a twofold greater risk of fracture among patients (age ≥ 50 years) with BD (271). In addition, a diagnosis of BD was associated with a 20% increased risk of fracture, independent of anticonvulsant use. Antidepressants and antipsychotic agents can similarly decrease bone mineral density (397). Screening for bone mineral density may be indicated in high-risk populations (398).

Closing statement

The purpose of this update is to add previously unpublished material to the CANMAT guidelines for the treatment of BD, ensuring that they remain current and practical. When a first-line treatment is unsuccessful, clinicians are advised to try alternative first-line treatments before proceeding to second-line options, and the same recommendation applies when second-line treatments fail. Judicious use of psychosocial interventions, alternative somatic treatments such as ECT, and the numerous experimental agents offer additional promise for the management of BD.

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